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Textbook of Psychological Medicine

Fifth Edition

The College of Psychiatry of Ireland



Brian O'Shea
Editor

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Edited by Brian O'Shea

DEDICATION

For Anne, John and Gerard and their families for their priceless companionship; for Gerald and Brian Cramp for their invaluable support; for James Coakley* for making the body interesting and understandable; for Michael G. Kelly* for my start in psychiatry; for Bryan Alton* for a good start in medicine; for Mark Hartman* who introduced me to the idea that unpaid work can be rewarding; for Jim Maguire* who made us laugh at adversity; and, for my parents Michael* and Theresa* for doing far more than their duty. (*RIP)*

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Preface

'In our times the field of science is broad and extensive and its increase on every side so rapid and so various that he who wishes not to be left completely behind must employ all his energies with continuous and unremitting assiduity'. (Robert Graves, 1864, p. 860)

This book started life back in the early 1980s as a very slim volume and expanded over the years. The College of Psychiatry of Ireland approached the author through its president Justin Brophy to make it available on-line. This request immediately struck the undersigned as being eminently more sensible than having it expand anonymously on his personal computer. Because of time constraints it has been decided to use those chapters that have been prepared by the author and to add other chapters (forensic psychiatry, intellectual disability, old age psychiatry, rehabilitation, psychotherapy with children, and child and adolescent psychiatry) when they become available. I hope that those who read the book will find it helpful when studying for examinations, when faced with clinical problems or as a resource for up-dating their knowledge of psychiatry. It is the intention of the writer to oversee the completion of the text by eliciting and editing the extra chapters. Thereafter he will hand over stewardship to the College of Psychiatry of Ireland with the sure knowledge that his endeavours will have found a good home.

A note on the title of the book is in order. This has been the title throughout the previous four editions. In recent years the Americans have adopted 'psychological medicine' for what we call consultation-liaison psychiatry. In an earlier (psychoanalytical) life this branch of psychiatry either did not happen or was referred to as 'psychosomatic medicine'. Other transatlantic differences in usage of terminology abound, e.g. 'learning disability' which has completely different meanings in the UK and the US. The College may eventually wish to change the title to something else.

I would like to thank those colleagues who have agreed to write additional chapters for this book. I would also like to express my thanks to Hemal Thakore for his help with the nuts and bolts of delivering the text to its readership. I would like to thank Justin Brophy for his encouragement. Justin described this undertaking as a "labour of love". I agree that the motivation needed was more likely of limbic than prefrontal origin!

I would particularly like to express my gratitude to Jane Falvey who was involved in the earliest editions of the book.

Most readers will not be intimately aware of the time required to research, write, and edit a work of this size but I can assure them that my family *is* aware – to them, for their patient sacrifice, I express my heartfelt gratitude.

Brian O'Shea
Editor
August 2010

Reference

Graves RJ. *Clinical Lectures on the Practice of Medicine*. Nelligan JM, ed. Dublin: Fannin, 1864.

Some reviews of the Fourth Edition of *Textbook of Psychological Medicine* (O'Shea B, 2002)

'I would recommend this book to trainees in psychiatry and although the text is primarily focused on the psychiatric membership examination, I feel it will find a place on many a physician's bookshelf in due course.'

Alan Byrne, *Irish Psychiatrist* 2003;**4**:71.

'... an invaluable reference source. Current research is critically appraised, and detail is attended to throughout, making this an extremely useful textbook for examination candidates. The style is relaxed and approachable....a user-friendly, practical reference source for any mental health professional in Ireland today.'

Emma Dineen, *Irish Medical Journal* 2003;**96**:157.

'..... this fourth edition is well worth the spend and every teaching library and practice in the country should make it available..... of particular merit is the rich historical detail that pervades each page.'

Maurice Guéret, *Medicine Weekly* 2004;**8**(1):48.

'It is packed with the type of information which appears in multiple choice examinations, but also tries to give the reader a thorough understanding of clinical concepts for use in everyday practice.'

Brian Ferguson, *Irish Journal of Psychological Medicine* 2005;**22**:37.

Referencing abbreviations

AGP, Archives of General Psychiatry; **AJP**, American Journal of Psychiatry; **APA**, American Psychiatric Association; **APAD**, Adult Psychopathology and Diagnosis; **APP**, American Psychiatric Press; **APPTCP**, The American Psychiatric Publishing Textbook of Clinical Psychiatry; **APPTP**, American Psychiatric Publishing Textbook of Psychiatry; **APPub**, American Psychiatric Publishing inc.; **APS**, Acta Psychiatrica Scandinavica; **APT**, Advances in Psychiatric Treatment; **BJP**, British Journal of Psychiatry; **BJHM**, British Journal of Hospital Medicine; **BMJ**, British Medical Journal; **BP**, Biological Psychiatry¹; **Cdg**, Cambridge; **CL**, Churchill Livingstone; **CmPsychStud**, Companion to Psychiatric Studies; **Cst**, Chichester; **CTETPsych**, Cambridge Textbook of Effective Treatments in Psychiatry; **CUP**, Cambridge University Press; **Dn**, Dublin; **DTB**, Drug and Therapeutics Bull; **ea**, et al; **Edb**, Edinburgh; **EEPpsych**, Evidence and Experience in Psychiatry (series); **EPMed**, Essentials of Psychosomatic Medicine; **FCP**, Foundations of Clinical Psychiatry; **GTPD**, Guidelines for the Treatment of Psychiatric Disorders; **Harv**, The Harvard Guide to Psychiatry; **HLPsych**, Handbook of Liaison Psychiatry; **HRB**, Health Research Board; **IJPM**, Irish Journal of Psychological Medicine; **IMJ**, Irish Medical Journal; **imt**, Irish Medical Times; **IPsych**, Irish Psychiatrist; **JAD**, Journal of Affective Disorders; **JAMA**, Journal of the American Medical Association; **JCP**, Journal of Clinical Psychiatry; **Ln**, London; **LOP**, Lishman's Organic Psychiatry; **LT**, Lancet; **MUP**, Melbourne University Press; **MGHHGHP**, Massachusetts General Hospital Handbook of General Hospital Psychiatry; **MGHCCP**, Massachusetts General Hospital Comprehensive Clinical Psychiatry; **MHC**, Mental Health Commission; **MW**, Medicine Weekly; **NEJM**, New England Journal of Medicine; **NP**, Neuropsychiatry; **NY**, New York; **OTOAPsych**, Oxford Textbook of Old Age Psychiatry; **OUP**, Oxford University Press; **Ox**, Oxford; **OxTxPsych**, Oxford Textbook of Psychiatry; **PB**, Psychiatric Bulletin (formerly Bull Roy Coll Psychiatrists); **PCMP**, Psychiatric Care of the Medical Patient; **Phld**, Philadelphia; **PMed**, Psychological Medicine; **PRA**, paper read at; **RCPsych**, Royal College of Psychiatrists; **SI**, Seminars in (book series); **SPDNEP**, The Spectrum of Psychotic Disorders: Neurobiology, Etiology, and Pathogenesis; **TPsych**, The Psychiatrist; **Txtbk**, text book of; **WDC**, Washington, DC; **WHO**, World Health Organisation.

Note: DOI numbers refer to the Digital Object Identifier System for identifying objects (such as journal articles, including those published ahead of print) in the digital environment. It is managed by the International DOI Foundation. For example the DOI reference for *Br J Psychiatry* 2009;194:434-8 is 10.1192/bjp.bp.108.052605. The letters *aop* stand for advance online publication.

Cautionary note

The reader is strongly advised to consult up to date data (indications, contraindications, precautions, interactions, side effects, toxicity, cost, etc) from reliable sources (e.g. manufacturers' data sheets, *Martindale*, *BNF*, *MIMS*, *Irish Drug Reference*, and *Irish Medicines Formulary – Physician's Desk Reference* in US) before prescribing medication.

The editor: Dr Brian O'Shea works as a Tribunal Psychiatrist with the Mental Health Commission. He was Clinical Director and Consultant Psychiatrist at Newcastle Hospital, Greystones, Co Wicklow, Republic of Ireland, until December 2006. He qualified from University College Dublin in 1974 and was a Consultant Psychiatrist at St Brendan's Hospital, Dublin for two years before moving to Co Wicklow in 1985. He has published c. 400 articles and was an examiner in all parts of the Membership Examinations of the Royal College of Psychiatrists in the UK for two decades. He is Editor of *Irish Psychiatrist*, a member of the Editorial Board of the *Irish Journal of Psychological Medicine*, and has acted as an Assessor for Irish, British and North American journals.

Other books by Brian O'Shea

A Textbook of Psychological Medicine. 4 editions (1985-2002)
Essays in Psychiatry. 2 volumes (1984, 1989)
Schizophrenia: The Cutting Edge. 2 volumes (1997, 1998)
Core General Psychiatry: 'Functional' Syndromes. (2007)

¹ In references only (BP refers to bipolar [affective] disorder in text).

Foreword

It gives me great pleasure to write the foreword of this fifth edition of the *Textbook of Psychological Medicine*. There are several remarkable aspects to this publication which makes it most welcome. This continuously revised textbook has been under the direct authorship and stewardship of Dr Brian O'Shea since its inception. This is a singular achievement and almost unparalleled in regard to contemporary medical publishing. The remarkable effort and diligence in compiling this work is a great gift to our speciality and Dr O'Shea deserves special thanks and regard by the profession in this light.

Also remarkable is the fact that he has without hesitation made it available as to be the first electronic textbook available to Irish psychiatrists through the offices of the College of Psychiatry of Ireland. Coming as it does shortly after the first year of its beginning, the College is extremely proud to have this work available to members and we feel it marks an auspicious and important beginning to our academic programme. The fact that it has been made available to members free of charge and that it is available in electronic format makes it particularly accessible.

The standing of the textbook is such that it is available as an open resource for all students of the discipline, introductory, those in training, and those undergoing continuous professional development. The high level of detail and scientific integrity makes it suitable to span all such needs and it is a most welcome addition as a medical resource of great scope.

Any single author textbook runs the risk of omissions, oversights, and imprecision. The textbook will remain under Dr O'Shea's editorship until the current edition is complete. At that stage, when he hands it over to the College, we expect to recruit editors of sections who will take submissions in regard to supplements, corrections and any other comments which will enhance the work. This marks a first in publishing of this kind and means that truly the textbook becomes the property of the profession and that the knowledge of peers and experts can be collected in one place for the benefit of all.

On behalf of the profession I would like to thank Dr O'Shea for his scholastic diligence and his exceptional generosity in agreeing to make this available at this time. We hope that it marks the beginning of what will be a truly wonderful resource for us all in the future.

Dr Justin Brophy
President - The College of Psychiatry of Ireland

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Assessing, Describing and Classifying Brian O'Shea

'You know, Charles, I don't like psychiatrists'. (Winston Churchill, February 19, 1953, in Moran, 1966)

'They said I was mad: and I said they were mad: damn them, they outvoted me'. (Nathaniel Lee, 1649-1692, Bedlam, quoted in Russell, 1997)

'...we must not lose the human face of psychiatry as it becomes progressively more scientific'. (Andreasen, 2001)

'Increasing complexity is accompanied by the potential for complex aberrations'. (Weller & Eysenck, 1992)

'No perspective on its own can offer a complete account of a patient's mental functioning'. (Szmukler, 2007)

This chapter focuses mainly on the fundamentals² of the initial psychiatric history and mental state examination. This process is both an enquiry and a therapeutic process. There are no short cuts and practice is essential. The relationship between psychiatrist and patient is a fiduciary one.³ Psychiatrists, like other clinicians, may be less proficient in essential clinical skills than they would like to imagine. (Maguire, 1993) This is despite the fact that 'Our most profound understanding is derived from the intermeshing of various parts of the patient's self with parts of ourselves.' (Giovacchini, 1990) A *therapeutic alliance* should be established and maintained with the patient. This is necessary in order to ensure a collaborative working relationship. Otherwise it may be more difficult to ask patients to undertake distressful measures, e.g. revealing a history of abuse, resisting hand-washing in compulsive states, facing feared circumstances in specific phobia or agoraphobia, ignoring certain behaviours of children, or suffering early side effects of psychotropics.

Comfortable seating and lack of disturbance are essential.⁴ After initial introductions (including your own name, title, and position), the interview proceeds. As in general medicine, observation⁵ is the keynote to success.⁶ Facial expressions⁷, unless consciously suppressed, reveal much useful information.⁸ Body language may unmask feelings that the face keeps hidden. (Elkman & Friesen, 1974)

A good medical communicator shows interest in the patient, elicits beliefs and concerns, acknowledges and responds to signs of distress, uses language the patient understands and gives information in digestible dosage, collaborates with and empowers the patient⁹, and maintains privacy and confidentiality. (Royal College of Physicians and RCPsych, 2003; Sholinghur, 2008; Murphy, 2009; RCPsych, 2009)

Some qualities of a good psychiatrist¹⁰

Prioritises patient care and does not take advantage of vulnerable others

Up to date, uses new research evidence wisely, works within limits of competence

² There are many short publications available that deal exclusively with the examination of patients, e.g. Casey ea.(2004) and, from a US standpoint, APA.(2006) Excellent advice for the old MRCPsych was to be found in Holden (1987,1990a) and Trigwell ea (1996) but the examination has changed greatly in detail over the years.

³ Based on trust.

⁴ Often lacking.

⁵ *Kinesics*: study of nonverbal gestural communication.

⁶ This becomes less obtrusive with experience.

⁷ Experienced clinicians, according to Ekman (1986) may detect fleeting 'micro-expressions' on a person's face (Spillane, 1983) that give away true but otherwise hidden feelings, such as the transient glimpse of despair in the normally smiling patient. It should be noted that one may have paresis of voluntary or involuntary (mimetic) facial movements so that a patient who cannot smile when asked may do so spontaneously when responding to a humorous remark. Loss of muscular tone may lead to vacant expression in GPI. Pendular eye movements plus rhythmic jaw movements (oculomasticatory myorhythmia) may found in Whipple's disease.

⁸ This repertoire of expressions is probably common to all cultures, and even blind children have very similar expressions to sighted ones. (Izard, 1971)

⁹ Empowerment and improved social networks may combat self-stigmatisation. (Brohan ea, 2010)

¹⁰ Adapted from RCPsych, 2009.

Gets on with people, respectful, good communicator, respects autonomy
 Good team player¹¹ and positive role model
 Willing to allow second opinion, consults other professionals as appropriate
 Respects a patient's right to be accompanied by carer, family, friend, or advocate
 Honest, trustworthy, acts with integrity, does not violate boundaries¹²
 Maintains confidentiality¹³
 Ethically attuned, including when involved in research
 Accessible when on duty/on call
 Uses resources available (prioritise based on clinical need) and presses for improvements when necessary
 Considered and measured approach when raising concerns about another professional's weakness
 Does not discriminate based on patients' contribution to illness (e.g. lifestyle)

It is important not to assume that patients who have reduced ability to show emotion (e.g. Parkinson's disease or the misleadingly 'calm' patient on an artificial respirator¹⁴) cannot over hear what one is saying about them (or other patients).

The psychiatric history, an outline

Demography: Name, address, age, marital status, and occupation.

Presenting complaint(s) and its (their) approximate duration. Details of these complaints may be elicited now or later.

Past history of psychiatric illness: Receipt of psychiatric treatment in the past: if so, where, for how long, by whom (GP, psychiatrist, psychologist, priest, counsellor, etc), and in what manner -e.g. psychotherapy, antidepressants, ECT, etc?

Past history of important physical illnesses, e.g. TB, rheumatic fever, amputation, and allergies.

Childhood: birth and early milestones; home or institutional environment; relationship between and with parents; relationship with and details (chronologically) of siblings and other close friends and relatives; so-called 'neurotic traits' (enuresis, nail-biting, nightmares, night-terrors, etc.)

School years: details of schools attended; reasons for change; relationship with teachers and classmates, attitude towards, and self-appraisal of ability to, study; truancy; school refusal and phobia; bullying, scapegoating; games played; exam results; feelings about level achieved; etc.

Employment history: jobs held; redundancies; periods unemployed and why; efficiency; pay; military duty; work abroad; relationship with employer, employees and colleagues; hopes for the future.

Social history: hobbies, pastimes; friends; social skills (literacy, driving of motor vehicle, dating, etc); tobacco, alcohol; other drugs. One unit of alcohol is roughly a half-pint of beer, a single measure of spirits or a glass of table wine.

Sexual/Marital: The experienced interviewer is more able to put the patient at ease. Do not start off this section with blunt questions about masturbation, infidelity, and sexual deviancy. Details of such matters as menstruation and the number of pregnancies should be elicited with a concerned but professional approach. Remember that pregnancy remains possible for the first couple of years after the commencement of the menopause¹⁵. *Empathy* (actively feeling with another whilst keeping own emotional perspective – distinct from identifying with) is superior to sympathy (feeling for). *Without empathy there is poor communication and little chance of treatment adherence.* Source of information on facts of life; attitudes towards sex and the sexes; puberty; menopause and climacteric; dating; sexual experience; marriage; children. Many trainees ask 'too little or too much' about their patients' sexual lives. (Kopelman, 1994)

Family history: Consider both parents' families. Details of psychiatric or serious medical/surgical problems. 'Did any one of your relatives ever suffer from nervous problems?' Draw a diagram of the family tree: ¹ for males and O for females, fill these in for members affected by the disorder in question, e.g. ■, put an oblique line through the symbol for members who are deceased, and use a double oblique line to indicate divorce.

System review: Enquire about changes, especially recent ones, in, for example, weight, appetite, sleep, sexual appetite (*libido* – in psychoanalysis this refers to 'psychic energy'), and ask questions about somatic systems.

Legal history: Get appropriate details: 'Have you had any dealings with the police?'

Some interviewing tips:

Single question: avoid multiple questions at one time – some may not be answered and they can be a source of upset, especially for the cognitively impaired.

Facilitation: help the interviewee to develop a theme; it can be verbal, anything from a grunt to a statement such as 'Perhaps you might expand a little', or non-verbal (smiles, movements of head or facial parts, postural shifts).

Empathic statement: an invitation to the patient to continue or expand on a theme, e.g. 'It must have a terrible experience'.

Clarification: question designed to find out what a person means by their statement, e.g. 'What do mean when you say you feel depressed?'

Negotiation: indicating that you wish to explore further with the client's permission, e.g. 'I know this may be upsetting for you, but it is important that I understand exactly how this matter has affected you'.

Recapitulation: feeding a summary of the subject matter to the patient, e.g. 'As I understand it, you...'

Exposition: explaining diagnosis and management and answering questions that arise.

¹¹ Collaborative approach; keeps patients' interests to the fore.

¹² Do not enter into a non-clinical relationship with patients or ex-patients.

¹³ **Clinical confidentiality** is the duty, extending even beyond death, owed by the clinician to safeguard private information given to him/her in trust by someone else.

¹⁴ Asking the patient to indicate 'yes' or 'no' or asking an experienced ICU nurse to lip read may be revealing.

¹⁵ In 2008 a woman in her late 50s was diagnosed with a 'tumour' – she had one: a baby!

Termination: ending the interview with appropriate statements or gestures; follow-up appointments, prescriptions, and other arrangements should be seen to be understood.

Mental state examination¹⁶

'There is a tendency for the literature to dichotomise normality and illness, whereas most disorders lie on a continuum of severity.' (Butler & Brayne, 1998)

'The skilled examiner often makes a diagnosis others have missed simply on the basis of looking carefully where others have neglected to look.' (Nicholi, 1999)

Trethowan¹⁷ & Sims (1985) remind us that 'Just as a knowledge of pathology is fundamental to the understanding of physical disease, so is a knowledge of psychopathology fundamental to the understanding of psychiatry'.¹⁸

Psychopathology, the study of abnormal mental states, can be divided into *phenomenological* (an objective description of findings), *psychodynamic* (inferring subconscious mechanisms), and *experimental* (do something to change one phenomenon and observe what effects this has on other phenomena, e.g. cognitive therapy to alter ways of thinking may change mood/affect) subtypes.

Mental state examination: basic outline

Get a general picture of his/her appearance and behaviour. Think about the way the patient talks. What does he say and how does he say it? (*content v form*) Record examples. *Mood* (how he feels; subjective, pervasive and sustained emotion colouring perception of the world – old English *mod* and German *mut*) and *affect* (how you evaluate his mood¹⁹) should be evaluated. What is the patient's current emotional responsiveness as witnessed by observer? It may be congruent or incongruent with mood). *Reactivity* is defined as the ability to temporarily alter mood under certain conducive circumstances, as when the patient becomes cheerful when told good news. Delusions are classically defined as false, fixed belief, held with conviction in the face of contrary rational argument or proof, not in keeping with past education or culture. Sims ea (2000) prefer to define delusions as 'overriding rigid convictions which create a self-evident, private and isolating reality requiring no proof'. Some authors believe that delusions are a defence against low self-esteem. (Lyon ea, 1994) Certainly, events may influence delusion content, e.g. Raune ea, (2006) in a study of first-episode psychosis, found that intrusive events were associated with persecutory themes, loss events were negatively associated with losses, and (counterintuitively) danger events (but not loss events) were associated with depressive delusions. In clinical practice it is not so much the falsifiability of the belief as the reasons given for believing it that signify the presence of a delusion. (Mullen ea, 2000)

Misinterpretations (illusions), hallucinations, so-called 'anomalous' experiences (e.g. alterations in colour, shape, size, loudness of real objects), obsessional thinking or compulsive acts, and experiences of unreality are sought. Orientation for time, place and person are examined. Immediate (repeat digits forwards and backwards), recent (what bus he got to the clinic, what was eaten for breakfast) and remote memory (birthplace, dates of world wars, famous public figures) are tested - short-term memory may involve activation of short synaptic circuits via neurochemical transmission; long-term memory may mean intraneuronal protein and RNA synthesis, which then contain a code. Also tested are ability to attend to what is going on and to concentrate on matters at hand (e.g. serial subtraction of 7s from 100 – if this is problematic use serial 3s or counting backward from 20; practice effects are overcome by serial 7s from 101)²⁰; general information (Taoiseach²¹, President, Queen of England, President of USA, where and what is the White House, capitals of major countries, date of ending of World War II - 1945, six large towns in Ireland or country of origin); general impression of the *intelligence* (ability to understand, recall, mobilise and constructively integrate previous learning in meeting new situations); *insight* (why does he think he is being examined by a psychiatrist or why is he being prescribed medication?) and *judgement* (what would he do if he ran out of medication some time before his next appointment, if he saw a house on fire or discovered a stamped, addressed envelope on the street?). In disorders where cognitive ability recovers (e.g. delirium) reorientation occurs in the following order: to person, to place, and to time. The rare *idiot savant* suffers from significant learning disability, autistic disorder, or Asperger's syndrome. (Goldstein ea, 2002) yet performs feats of memory, computation, or puzzle solving in sharply circumscribed intellectualised areas, such as telephone numbers. However, such feats are not translated into positive life change.

Memory

Memory, retained learning and experience, can be divided into: *short-term or primary* - limited capacity; does not require understanding of material; decays rapidly if not rehearsed; displaced by new input; test with digit span (probably of limited value; can be intact in advanced dementia; concentration-dependant; schizophrenic patients may disengage from strings of digits that are shorter than controls can engage with:

¹⁶ The first person to use the term mental 'status' examination appears to have been Adolf Meyer in 1918. (Nicholi, 1999)

¹⁷ Sir William Henry Trethowan (1917-1995), London-born professor of psychiatry at Sydney and (emeritus) Birmingham, with special interest in unusual psychiatric disorders and social anthropology.

¹⁸ A sentiment echoed by Mullen. (1997) See (Casey & Kelly, 2007) for an overview of psychopathology.

¹⁹ Latin *affectus*, mood. Unfortunately, some authors use these terms differently, e.g. *mood* as the enduring feeling state (like climate) and *affect* as observed or patient-reported present/cross-sectional feeling state (like weather).

²⁰ These are tests of attention, not of mathematical prowess and so should be pitched at the patient's educational level.

²¹ Prime Minister, Republic of Ireland.

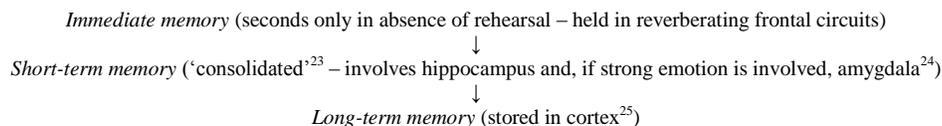
Keefe, 2003); and *long-term* - encoded mainly as meaningful concepts; durable; or, as is usual clinically, *immediate (working), recent and remote*. (Note: different authors classify memory differently, e.g. Sims [2003] divides it into immediate ['sensory store' – held for < 1 second], short-term/primary/working [15-30 seconds; tested with digit span, and long-term/secondary [minutes to decades].)

Alternatively, it can be classified as *episodic* - for specific events, such as a telephone message, or *semantic* - for understanding words, concepts and facts, e.g. who was Ireland's first female president (?) or name all the animals you can in one minute, or *implicit* - for automatic²² skills, e.g. driving, grammatical speech. Asking the patient to recall words can test *explicit* (i.e. consciously known) memory, and implicit memory can be tested using a word-stem or word-fragment completion task.

Semantic and implicit memory do not decline with age; knowledge increases throughout life; there is a small decrease in episodic information over time, possibly because of reduced frontal lobe function.

Working memory, an elaboration of short-term memory, (Lishman, 1987) is used in solving and understanding problems, i.e. brief storage of information in the service of current cognitive activity; a limited amount of data is kept immediately accessible for current employment or manipulation. It consists of an articulatory/phonological loop (holds data in mind by using subvocal speech), a visuo-spatial scratch pad (maintains data as visual images), and a central executive (directs 'slave systems' such as visuo-spatial scratch pad and articulatory loop). (Baddeley, 1986)

Management of impaired memory may involve compensatory mnemonic strategies (overt/covert rehearsal, organisational approaches, use of visual imagery, etc), external aids (e.g. notebooks, electronic organisers, notice boards, etc), special teaching methods (acquiring specific skills and knowledge specific to a domain – utilises implicit learning ability), and drug therapy (e.g. anticholinesterases after traumatic brain injury or thiamine in alcoholics).



Pre-morbid personality²⁶

Get a thumbnail sketch of the kind of person he was before this present problem arose.²⁷ The patient may lack insight²⁸ or be psychotic and therefore give an inaccurate account of his pre-morbid personality. Many

²² I.e. one is not necessarily conscious of having remembered something. People with an amnesic syndrome can learn how to do certain things or how to approach certain problems without being aware of having done so. *Procedural memory* (e.g. remembering how to ride a bicycle) is one type of implicit memory; it is dependent on frontal lobes, cerebellum, and basal ganglia but not the hippocampus; it is particularly affected by subcortical dementia.

²³ Protein synthesis and development of dendritic connections. Is the notion of **consolidation** of new experiences correct? Cueing patients with amnesic syndrome may improve performance. They may perform better on recognition tests than during free recall. Also, as pointed out by David and Kopelman (2009, p. 38), lack of consolidation as a reason for extensive retrograde amnesia would infer that consolidation takes many years to occur!

²⁴ The **amygdala** is involved in encoding fearful memories and aversive conditioning. Both fear (acute, external threat) and (anticipatory) anxiety are included here. Fear activates the sympathetic nervous system via the locus coeruleus giving rise to physical symptoms such as tachycardia. Fear awareness is a property of the (especially frontal) cortex. The cingulate cortex mediates activity between cortex and deeper structures.

²⁵ This may be hippocampus independent and the cortical location depends on the sensory modality involved.

²⁶ **Questions about pre-illness personality functioning:** Worrier; moods & consistency of moods; finds it difficult to make/keep relationships; finds it hard to express feelings; violent; independent; assertive; can plan ahead; hopes/ambitions; hobbies/interests; view of self; reactions to stress; abuse of tobacco, alcohol, drugs; able to tolerate frustration; and can learn from experience?

²⁷ In his own eyes and in those of his friends and not so friends.

²⁸ Schizophrenic patients may have full insight, be aware of being ill but misattribute their symptoms, or be unaware of being ill. Mysore ea (2007) found misattributing group to be cognitively intact but the unaware group to be impaired on executive and memory tests. Karow ea (2007) found better insight in schizophrenia was associated with subjectively worse quality of life and greater integration into social networks. According to Haq ea (2008) insight is poorer during phases of psychosis associated with positive symptoms and improves with their disappearance, a surmise, as the authors admit, that needs to be tested in longitudinal studies. Unsurprisingly, Haq ea (2009) found, in stable schizophrenic and schizoaffective patients, that there was a significant negative relationship between attitudes to medication and delusions and a significant positive relationship between insight and attitudes to medication. Bajaj ea (2009) found that insight and compliance were positively related to each other and both of these were negatively

patients describe themselves as having been 'outgoing with plenty of friends', which should be checked against other information given during history-taking. The patient may have been ill for a very long time²⁹ or have had multiple recurrences. Depressed people may describe themselves in a bad light.

There are two chief sources of information about how the patient functioned before the onset of illness: the patient himself and *collateral (corollary)* information.³⁰

A physical examination³¹ may be necessary, especially if the patient is being admitted, (Byrne, 2007) if there are new/acute/suggestive complaints or signs, the patient belongs to a high risk category (e.g. substance use), for medico-legal purposes, and so on.³² The nervous system is often poorly assessed or even ignored.³³ (Hughes, 1991; Mitchell ea, 1998; Garden, 2005) The general practitioner (GP) may be telephoned for more facts.³⁴ Blood tests³⁵, X-ray examinations or other ancillary tests may be required.

related to psychopathology scores in a four-week longitudinal study of patients with schizophrenia in India. Supernatural explanations of symptoms are common in the East. (Saravanan ea, 2007)

²⁹ Schizophrenia often causes gradual change over years before presenting 'acutely'.

³⁰ From people who know him well, a home visit, social worker report, previous psychiatric or medical files, and, often forgotten, the general practitioner. The Community Psychiatric Nurse is often a mine of information on the family. (Tyrer ea, 1990)

³¹ See, e.g. Ogilvie and Evans (1997) and Forbes and Jackson. (1997)

Permanent tattoos are more common among psychiatric patients (and other 'marginalised' groups such as prisoners) than in the general population. (Khosla ea, 2010) Adolescents, often impulsively, may seek a tattoo only to regret it later. Requests for removal may reflect poor self-image or to appear more professional in occupational endeavours. Owners of tattoos are at increased risk for impulsiveness/risk-taking, self-harm, alcohol/substance-related problems, and personality disorders. Apart from the usual somatic complications such as keloid and infection, tattoos may be associated with swelling and a feeling of burning during MRI (metallic pigments). Detained patients who lack competence should be protected against being tattooed.

³² Factors that should suggest a somatic disorder include acute onset, abnormal vital signs, physical symptoms or focal neurological signs, youth, older age, no past psychiatric history, hallucinations other than auditory, and disorientation. (Reeves ea, 2000)

Schizophrenic patients are often neglected as far as their significant physical morbidity is concerned. (Meyer & Nasrallah, 2003)

³³ The locomotor system is equally poorly investigated. (Garden, 2005) A **brief neurological assessment** should include: ability to stand, feet together; walk forward/backward heel-to-toe with eyes open; walk on tiptoes and (later) on heels; hold arms outstretched with palms upwards for some seconds; touch nose with tip of index finger with eyes closed; repeat last movement with middle finger; perform piano-playing movements whilst arms are outstretched; pat dorsum of each hand with opposite palm; close eyes tightly; grin; stick out tongue; wiggle tongue; stare at examiner's face while examiner wiggles a finger in each outer quadrant on one side and then the other and then both sides simultaneously (patient points to finger/s); holding head still, follow examiner's finger across midline and up and down; test reflexes with legs dangling from couch; funduscopy; and anything else that is indicated (e.g. examination of tympanic membranes). Deep tendon reflexes: biceps C5/6; brachioradialis C5/6; triceps C6-8; knee (quadriceps) L2-4; and ankle (gastrocnemius) A1. The finger jerk or reflex (C8) is performed by having the patient gently curve his fingers over your index finger; now raise your hand and then tap briskly on your fingers; the patient's fingers should flex. Tendon reflex reinforcing techniques include the Jendrassik manoeuvre: patient's fingers of both hands grasped together and attempting to pull hands apart with palms facing each other. Remember that muscle rigidity of the clasp-knife variety is associated with upper motor neurone lesions; basal ganglia disease gives rise to cogwheel or lead-pipe (does not vary along whole range of joint movement – can be tested for by asking the patient to mimic screwing in a light bulb by quickly rotating the wrist in alternate directions) rigidity. Asking the standing patient to drop his arms to his sides may screen for EPS: the rigid side will fail to bounce off the side. Asking a person to draw circles in the air with one arm while the opposite elbow is checked for cogwheeling is a useful trick. It should be noted that spasmodic dysphonia, a focal dystonia of the larynx, causes a choking or whispered voice depending on involvement of adductor or abductor muscles respectively. Hemiatrophy may be present in one palm in cases of early brain damage.

A rough examination of the **cranial nerves**: I (smell), II (acuity [Snellen chart or Rosenbaum card], fields [confrontation], discs), III + IV + VI (pupillary reflexes), III + IV + VI (eye movements – III nerve lesions in diabetes are associated with intact pupillary reflexes because the pupillomotor fibres are unaffected), V (jaw strength, sensation in face), VII (movement of face), VII (hearing), IX + X (palate), XI (shrug shoulder, rotate head), and XII (move tongue). Poor visual acuity may be implicated in visual illusions or hallucinations. *Gaze-evoked nystagmus* is the presence of nystagmus when the eyes are held for several seconds at the extreme of movement in one direction; it can be caused in both directions by ethanol, sedative-tranquillisers, and anticonvulsant drugs. Normal *saccades* are involuntary, rapid, conjugate changes in eye position between fixations: to test saccades the patient stares at the examiner's nose, then quickly looks at your finger, and then back at the doctor's nose; repeat this test with your finger in up, down, left, and right. Central facial weakness spares the forehead whereas peripheral (VII nerve or facial nucleus) affects the whole hemiface. Testing speech sounds: 'pa' = labial (lips), 'ta' = lingual (tongue), and 'ka' = palatal.

Horner's (or Claude Bernard-Horner) syndrome (ptosis, meiosis, anhidrosis, apparent enophthalmos, and loss of spino-ciliary reflex [pinching skin of neck should lead to ipsilateral pupil dilatation; a weak reflex but if present it is against diagnosis of Horner's]) was described by the Swiss ophthalmologist Johann Friedrich Horner in 1869. The cause may be anywhere along the sympathetic pathways (making it a poor localising sign) and can be congenital or acquired (including iatrogenic). The lesion is ipsilateral to the abnormal findings. Among the many causes are multiple sclerosis, lateral medullary syndrome, cavernous sinus thrombosis, syringomyelia, sympathectomy, cervical plexus/stellate ganglion/interscalene block, thoracostomy, neck trauma, goitre, carcinoma of thyroid, cervical rib (pulling on stellate ganglion), Klumpke's paralysis, neurofibromatosis type I, cluster headache (the combination = Horton's headache), middle ear infection, Pancoast tumour of lung apex, carotid artery dissection (Horner's syndrome contralateral to hemiparesis: disrupted carotid sympathetic plexus), and thoracic aortic aneurysm (including dissecting).

³⁴ 'Face-to-face contact or a telephone conversation between two doctors caring for a patient can often do more than an exchange of lengthy, repetitive, albeit academically brilliant summaries.' (Cybulska & Rucinski, 1989)

Psychometric studies (psychologist) may be ordered as appropriate. It is not appropriate to rely on psychological tests to make a psychiatric diagnosis. You cannot, for example, ignore clinical context and diagnose from MMPI results. Medically ill patients tend to score high on Hy (hysteria) and Hs (hypochondriasis) scales. (Wise & Rundell, 2005, p. 225) Nursing observations and old case notes may be available and should be consulted.

Infections of the CNS should be considered in the differential diagnosis.³⁶

Nurcombe (2008, p. 1) points out that a good diagnostician matches the pattern of elicited phenomena to the best-fit 'idealized' disorder (commonality allowing generic therapeutic plan) whilst also seeking reasons why this individual person got and continues to have their problem (uniqueness allowing individual adaptation of treatment).

Finish with a *formulation*, a brief summary of the case, differential diagnosis, prognosis, and plan of management, noting positive points only.

Interviewing

'Most mental disorders affect the young and are chronic, recurring illnesses that last a lifetime'. (Michels & Marzuk, 1993)

(a) General.

The interview is a deliberate, non-haphazard process, demanding an understanding of psychopathology and psychodynamics (*vide infra*). Psychopathology may be more obvious with the patient in a familiar environment rather than in the clinic; there may be an apparent 'remission' in hospital, followed by 'relapse' on discharge. (Naguib, 1991) The interviewer demonstrates sensitivity, skill and tact.

Allow patient reveal private thoughts without feeling demeaned
 Patients vary in the degree and timing of revelation and concealment of factual material
 Some patients will be hostile, perhaps (but not always) because they are of involuntary legal status
 Good rapport imparts a therapeutic feel to the encounter
 Interviewer and interviewee should achieve a shared understanding
 Trainees should stick to a set order of questioning
 Flexibility, although not always desirable during a first session, is an acquired art
 Keep interruption to a minimum, and handle it tactfully when it happens
 Settings will vary: office, high security or general hospital ward, busy clinic, or, all too often, a window-seat or linen-cupboard
 Every effort should be made (comfort, lighting, etc.) to acquire a setting conducive to good interviewing
 Note taking³⁷ should be explained ('Do you mind if I write as we speak?') or re-written from brief pointers later; it should be as unobtrusive as possible and serve the dual purpose of aiding recall and a form of communication with others
 Interviewer should be aware that client may request recorded information
 Some patients may feel neglected whilst you write
 More notes will be necessary early on
 Later, only new information needs recording
 Emotional responses of both parties should be noted
 Manner in which interviewer interjects (grunts, verbal acknowledgements, shifts in body posture) may influence relationship for good or bad

³⁵ E.g. **prolactin** level: hyperprolactinaemia is raised by sleep, sexual intercourse, significant stress, pregnancy, lactation, renal or hepatic failure, hypothyroidism, opiates, oestrogens (including anovulants), dopamine antagonist drugs (e.g. phenothiazines, risperidone, domperidone, metoclopramide – dopamine agonists usually shrink prolactinomas), prolactinoma (very high levels are strongly suggestive, e.g. > 5000 mU/L with macroadenoma and > 2000 mU/L with microadenoma), acromegaly (prolactin co-secretion), compression of pituitary stalk, seizures, polycystic ovarian syndrome, and idiopathic cases. Whilst most antiemetic drugs raise prolactin levels, cyclizine does not. Galactorrhoea is not synonymous with increases in prolactin (e.g. duct ectasia). Extremely high prolactin levels may give a falsely low reading due to the 'hook effect' but dilution of the serum will reveal the hyperprolactinaemia. Macroprolactinaemia refers to high molecular weight complexed prolactin + IgG which is inactive – it does not require intervention but can be misleading: 'apparent hyperprolactinaemia' - after precipitation of IgG with polyethylene glycol the prolactin level can be measured accurately and shown to be normal.

³⁶ CSF findings with such infections include polymorphonuclear cells with bacterial infection and increased lymphocyte counts with viral (incl herpes simplex encephalitis), TB, and syphilitic meningitis; lowered glucose levels with bacterial, TB, and syphilitic meningitis (normal with viral meningitis and herpes simplex encephalitis); and protein levels greater than 150 mg/dL in bacterial and TB meningitis (less than 100 mg/dL in viral and syphilitic meningitis and in herpes simplex encephalitis).

³⁷ Casey ea (2004, p. 6) suggest note taking during the interview whilst Schiffer & Lajara-Nanson (2003, p. 4) condemn this practice! Common sense and context should dictate. Note taking has medico-legal significance.

Interviewer forms understanding of stage of illness being dealt with and any effects of treatment³⁸
 Number of interviews required for proper evaluation should be discussed with the patient
 Depth of material that can be elicited varies, e.g. some patients need many interviews before getting to the kernel of the problem, or before the therapist can formulate the problem and decide on management

The interviewer should ask himself many questions: How much encouragement, reassurance, advice, interpretation, indulgence, limit setting, or questions (even if these amount to subtle suggestions) should he direct toward the client? How long should this interview last? Is the setting private (e.g. office) or public (e.g. clinic)? There will be many variables to contend with, such as lateness, privacy, and seating arrangements. Questions should follow appropriately, e.g. do not enquire about intimate sexual details or pastimes just after discussing a recent bereavement. Remind the patient that you must know more about him if you are to be helpful.

Some clients demand immediate gratification, e.g. tablets, extra time, greater attention. The interviewer must choose the correct time for gratifying or interpreting (e.g. an infantile need). If you are asked a personal question use your intuition. This will often reveal much about a client's motivation. You might say: 'Why do you ask that question?'

Resistances

May interfere with progress, even in the most motivated patient
 He may go silent, intellectualise, stick to symptoms or some other aspect of the history, or get annoyed
 He may continue talking or asking questions of you
 He may be seductive or resort to lateness³⁹

Do not take over the interview for the patient. Encourage spontaneity. Explain to him how matters are progressing from your viewpoint rather than interpreting in an analytical sense.

Try to understand the patient's socio-cultural background, how it differs from ones own, and also know your own personality. Experience, especially under supervision, with a wide range of patients is important. You can learn from your own conscious reactions to a patient⁴⁰. Deal with his emotions openly and honestly.

Defence Mechanisms

We all use defence mechanisms ('mental' mechanisms). Defence mechanisms are unconscious psychic activities used to reduce anxiety and eliminate conflict⁴¹. They are deemed abnormal if used too often, if they are used inappropriately (avoidance of reality testing⁴²), or if they fail to work. *Theory of mind*⁴³ is the ability to attribute mental states (e.g. desires) to oneself or others as a means of understanding and predicting behaviour. Simply knowing that ones delusion is not shared by others does not lead to insight.(McCabe ea, 2004) Examples of defences include:

³⁸ Treatment is a very broad canvas, ranging from counselling to drugs (licit and illicit, prescribed drugs, over-the-counter drugs, vitamin supplements, and herbal drugs – see Dunne, 2009).

³⁹ Freud divided up resistances depending on the assumed part of the psyche they originated from: conscious ego (e.g. the client is ashamed to reveal certain facts), ego (divisible into repression, transference, and secondary gain [elicitation of nurturance]), id [despite repeated interpretation the client repeatedly brings up the same material], and superego (e.g. will not relinquish symptoms because they serve as a punishment of the self).

⁴⁰ Are these reactions he evokes in most people. What are your personal reactions? Do they stem from the subconscious (countertransference)? Do you need his approval? Are you being consistent? Do you overidentify with him? Do you feel angry? Is there a power struggle? Are you intellectualising, and avoiding emotional aspects of the interview? Martindale (1987) discussed the excessive use of defence mechanisms within the families of patients with Huntington's disease and amongst those professionals caring for them. He argued that genetic counselling was not offered to these people and that this might help to spread the condition through to the next generation.

⁴¹ There are many **conscious** ways in which people attempt to deal with stress, e.g. humour (including 'gallows humour' – forbidden wish is verbally expressed but not enacted), stoicism, spiritual solace, seeking help from others, seeing it as a challenge and opportunity for psychological growth, employing relevant personal past experience, relaxation techniques, exercise, sports, and avoidance by withdrawal or distraction.

⁴² **Reality testing** is the objective evaluation of the world outside the self, including the capacity to see the self and others realistically. The ability to objectively test reality is a continuous variable, e.g. a severe case of paranoid personality might be more impaired in this regard at one point in time than, say, a person with schizophrenia of mild severity.

⁴³ **Theory of mind:** Psychologists have divided this into 3 orders: first, what one thinks is going on in one's own mind; second, what you think is going on in another person's mind; and third, what you imagine the other person thinks that you are thinking.(Brüne & Brüne-Cohrs, 2006) Connectivity between insula and anterior cingulate cortex may be an important determinant of ability to correctly sense what other people are thinking or what they believe.(Di Martino ea, 2009)

Reaction formation - person reacts to an impulse⁴⁴ (e.g. to kill) with the opposite behaviour or attitude (e.g. by sending Christmas presents). Mothers who smother their offspring with love may in fact harbour hateful feelings for them at an unconscious level.

Repression - vide supra - important to all unconscious defences - unbearable ideas and impulses are relegated to the unconscious mind (not the same as suppression which is conscious 'forgetting'); the concept of repression has been attacked by Merskey (1995) as (a) been used unethically to produce 'memories' of abuse in infancy, and (b) something for which real evidence is lacking.

Overcompensation - exaggerated correction, e.g. feel inferior so acts the bully

Identification – the unconscious counterpart of imitation; important in personality development (various subterms used like internalisation, introjection, and incorporation) - behaviour and attitudes modelled after another person. For example, in introjection (another's qualities taken as part of self) a person might assume aspects of the deceased in order to mitigate loss.

Regression - vide supra - reversion to earlier developmental level of functioning; common during admission to hospital.

Counterphobic behaviour - approaches fear instead of avoiding it - the claustrophobic (fear of enclosed spaces) becomes an elevator mechanic.

Intellectualisation - avoids facing up to feelings by hiding behind logic; unpleasant thoughts remain conscious whilst associated feelings remain unconscious, a derivative of *isolation of affect*.

Rationalisation – the giving of apparently logical reasons for beliefs or actions when really attempting to conceal true motives; the person who hits his wife avoids the painful reality that it was wrong to do so by deciding that she deserved it because of nagging!

Substitution - replacement of a seriously dangerous impulse with something impersonal and less dangerous, e.g. saw up wood instead of the mother-in-law!

Displacement of affect - the office boy who is annoyed by and hence hostile towards his boss beats his own wife up instead of the boss - not socially acceptable - also the basis of transference reactions.

Sublimation - aggressive and sexual desires diverted into socially and personally more acceptable channels, e.g. kicking a football instead of the boss!

Conversion - unconscious conflicts are given external expression in the form of physical ailments, such as hysterical paresis (hysterical conversion symptoms work via the voluntary nervous system, whereas the somatic symptoms of anxiety - such as palpitations - work via the autonomic nerves). A lack of concern, or *la belle indifférence*, may or may not be present in cases of conversion; anyway, it can also be found with general medical disorders, e.g. multiple sclerosis with frontal lobe involvement. (Raskin ea, 1966; Stone ea, 2006) Conversion disorder may, in fact, be accompanied by depression or anxiety. Cases of hysterical stupor tend to look toward the floor if turned on one side. Patients who appear to have a paralysed limb may have normal deep tendon reflexes.

Dissociation - occurs in hysterical amnesias, sleepwalking, loss of memory with running away (= fugue), and multiple personality - mental function(s) are split off from the rest of the personality.

Retroflexion - either sexual feelings are turned inward leading to excessive love of self (narcissism after Narcissus) or hostility is turned inwards leading to depression or a poor self-image.

Acting out - expressing unconscious conflicts in a manner not consciously recognised as such, e.g. prostitution or delinquency.

Isolation and undoing - compulsive rituals of the obsessive-compulsive neurotic consist of impulses which have become separated from unacceptable impulses, e.g. hand-washing instead of murder or rape (= isolation); atonement for guilt (= undoing), e.g. hand-washing because of past masturbation. Such rituals offer no pleasure. Macbeth tried to wash away Duncan's blood!

Projection - unacceptable wishes or impulses in the self are attributed to others⁴⁵; these wishes or impulses may be experienced as being directed back at the self.

Projective identification – described by Melanie Klein and extended by Wilfred Bion; (Meissner, 1999) good and bad aspects of self are split off and projected into someone or something (e.g. a doll) else; these aspects later become representative of and identified with these split-off parts; the person then tries to gain

⁴⁴ An **impulse** is a maladaptive behaviour that the subject is attracted to or feels obliged to carry out. It is associated with release of tension or with gratification/satisfaction/pleasure.

⁴⁵ 'Accusation is so often confession' (Browne, 2008, p. 32)

control over these parts by asserting control over the person (or thing) into whom they were projected; the person identifies with the object or tries to elicit a response in the object corresponding to the qualities of the projection; common in borderline personality disorder.

Denial - can accept at intellectual level that something has happened, such as a loss through death, but this is rejected emotionally; in delusional states intellectual acceptance is also forfeited so that the dead person is believed to still live, despite irrefutable evidence.⁴⁶

Splitting – strict separation of good and bad aspects of self or others in order to avoid having to cope with ambivalent feelings such as love and hatred.

Why does the patient want to see a particular doctor? Discuss this with the patient. Did he see other doctors before and how did he get on, and why did he stop seeing them? Learn about the patient this way, and try to give him insight indirectly. What does the patient expect from you: a listening ear, tablets, or rejection?

Telephone the GP⁴⁷ for further information. Contact relatives as required, being careful not to contravene the trust placed in the relationship between doctor and patient. Read previous notes and the referral letter. Does the information being collected constitute a true reflection of the client, and, if not, why not? Question any nurses who have dealings with the client.

What was the patient doing while waiting for you? Who accompanied him? How long did he set aside for the interview?

The presenting complaint may be dealt with at the start or end of history- taking as seems appropriate. The patient may wish to take the lead here, or it may be necessary to get early information on his background in order to put the problem in perspective. He should have some time at the start to ventilate. He should know that it is from him that you want to hear the story, not just from the referring letter. The latter vary in quality.

Avoid expressions of boredom/horror

Evasiveness may stem from shame

Guilt may lead to a confession

Help patient to confide and express feelings

Ask how he feels and what he finds difficult to communicate

Remind him of confidentiality⁴⁸

In manipulative cases⁴⁹ the true reason for consultation may only emerge if you bring up the subject, or the patient may reveal it as he leaves

Ask for examples rather than accepting bald statements

Seek patient's actual reactions to circumstances

Do not argue

Find out how symptoms affect patient's/other's lives

Move smoothly between topics

Try to get an idea of his personality. How does he spend his average day, get on with other people, respond to adversity, seem to other people, see his role in life, and feel about his status? Inconsistencies should be pointed out gently, e.g. 'I'm somewhat confused'. You may feed back statements verbatim. Most questions are best left open-ended, although clarification may sometimes necessitate the use of direct questioning. Direct questions can give misleading answers, especially in suggestible clients. Sensitive topics⁵⁰ require tact. You may need to wait for leads from the patients or ask indirect questions. A twenty year-old loss may be easier to talk about than a recent one.

Sometimes it may be necessary to put *mild* pressure on the client to elicit his feelings. Extreme pressure might prove problematic, e.g. a catastrophic reaction (*katastrophenreaktion*) in the early dement as described by Kurt Goldstein (1942). Be as gentle as possible, providing reassurance and explanation. Estimate how much stress the patient can tolerate by close observation, and allow him to recover his composure before leaving.

⁴⁶ 'What an asset his optimism is! It keeps out the facts': Lord Moran (Sir Charles Wilson) on Winston Churchill, November 10, 1953, in Moran.(1966) A famous example of denial is that of Anton Chekhov (1860-1904, Russian physician and writer) who persisted in writing that he did not have tuberculosis despite his chronic cough and regular haemoptysis.

⁴⁷ Letters from GPs tend to be deficient in several areas, e.g. prescribed medications and medical and social background.(Pullen & Yellowlees, 1985; Smith ea, 1994) A study of why Dublin GPs referred patients(Maguire ea, 1995) found that 30% were for specialist treatments, 20% due to failed treatment, 14% in order to share 'chronic care', and 13% to hand over care completely.

⁴⁸ In murder cases you should ask to see files, Book of Evidence, etc. With the move of psychiatry into the community and the consequent dispersal of paper-based information the need for electronic information sharing is becoming more relevant, particularly regarding potential for self-harm, alerts (e.g. allergies), and medication.(Feeney & Moran, 2007)

⁴⁹ E.g. a request for a letter for the local housing department initially disguised as 'depression'.

⁵⁰ E.g. salary, sexual habits, or past imprisonment.

He may have questions to ask which have not come up during the interview. These may reveal much about resistances, personality, expectations, attendance, and compliance. Discussions of treatment, diagnosis, prognosis or family diatheses should be tempered with hope and a promise to help in the future. A plan of treatment may be outlined and discussed. It is often best to avoid giving labels (e.g. paranoid personality disorder) to the patient unless they are accurate and adequate preparation has been made.

Second and subsequent interviews allow for a longitudinal study of the client, the monitoring of progress, checks on the effects of drugs, psychotherapy, and so on.⁵¹

Interviewing relatives is a matter of some skill and practice. The confidences of the client need to be upheld. The law allows us to violate confidentiality in some cases; where possible you should discuss the importance of these issues with the patient. You should discover what understanding of the client's problem(s) the relatives have. Do not take sides. You may advise the relatives on how to help constructively. One might see the patient first, then a relative, then both together. A common problem arises when various relatives (including in-laws) call at different times. This requires expert handling.

(b) Psychiatric history

'In spite of the pace of study in the biological aspects of psychiatry, it remains almost exclusively a clinical specialty.' (Casey & Craven, 1999)

Examination of the mental state is going on all of the time but is examined formally later.

The objective is to elicit as much information⁵² as possible about the client, to help us to understand his development as a person and the forces acting upon him as well as his influence on others, to understand his presenting problems against this background, and to act as a record to which we or authorised others can refer back to later.

Special problems encountered are language, interpreters, diminished consciousness, mutism, hostility, the hospitalised patient, and minors.

Allow the patient to state his reasons for consulting and his chief complaints in his own words for a reasonable period of time. Interrupt only in certain circumstances, e.g. obsessional rambling. Verbatim quotes are superior to jargon.

Record the source(s) of information, such as a relative in the case of dementia, and a description of the confidant. Think in terms of *predisposing*, *precipitating*, and *maintaining* factors. Give a description of the patient which would enable a listener/reader to feel that the patient was there in front of him: setting, appearance, behaviour, etc.

Why are you seeing him now, as distinct from any other time? When did his problem(s) begin and how was he functioning prior to that? What were his circumstances then? How has it/they affected his activities/personal relationships?

Get details of past episode of emotional/mental disturbance - symptoms, course, management, and outcome. Due to internal conflict, people often seek out situations that frustrate. Look for evidence of this recurrent theme in people's lives.

Get some idea of his home of origin, the nature of his birth, the attitude of his family to his arrival and its effect on others (e.g. unwanted pregnancy, sibling rivalry), problems during the pregnancy and neonatal period, and the presence of any feeding problems. Was there any head banging, body rocking, febrile convulsions, etc? Who reared him? How did he get on with members of the household, and how did he respond to strangers or separation? Were there any so-called 'neurotic traits' (e.g. nail biting, nightmares, and enuresis)? Did he experience problems in toilet training, which may reflect *temperament*⁵³ and/or parental attitudes? Were there any deaths in the family? Did bereavement reduce parental ability to give emotionally to the child? Was their lack of support made up for by others? Was there role-reversal - having to take over the parental role? What was he like in the early years? What games did he play and how did he get on with others? Could he tolerate frustration? Was he able to entertain himself or did he have frustration, boredom, tantrums, whining, silences, imaginary friends, etc?

Go through his childhood chronologically.

Childhood⁵⁴

Who was the disciplinarian at home?

Home and school atmosphere?

Early school experiences and relationship with peers and teachers?

How did he learn to read, speak, write, calculate, walk and run, and their timing?

⁵¹ Assessment for diagnosis or suitability for certain treatments, such as deep psychotherapy, may require a number of interviews. Psychotherapists often speak of the '55-min. hour', each session lasting 55 minutes. Information received at a first interview may require clarification and reactions to the interview may need to be discussed. More intimate details may be offered with time.

⁵² *Anamnesis*: developmental history of patient and his illness. *Ontogenetic*: pertaining to development of the individual. Piaget championed the idea that *ontogeny* recapitulates *phylogeny*, i.e. individual development reflects species development.

⁵³ Constitutional tendency to react to stimuli in a particular way; component of personality that is heritable, developmentally stable, based on emotion, and immune to social/cultural influence.

⁵⁴ Under Irish law a child is anyone < 18 years of age unless they are or were married.

Cruelty or phobias?
 Heroes?
 Fear of the dark?
 Truancy?
 Alcohol or drug abuse, tobacco, fire setting, problems with weight, or difficulties with assertion?
 Subtle hints of physical or sexual-abuse?
 Puberty: feelings, preparedness, and reactions?
 Masturbation and associated fantasies (tactfully)?
 Embarrassment re secondary sexual characteristics and attempts at concealment?
 Attitudes toward opposite sex and dating?
 Role, if any, of religion in the family?

Occupational history

Jobs: nature, responsibilities, dates?
 Periods of unemployment?
 Relations with bosses/workmates?
 Reasons for leaving/changing jobs?
 Feelings about current job?
 Occupational goals?

Ask about his social activities - loner, hobbies, pastimes, feelings experienced when in company, and sports.
 Has he any sexual difficulties - premature ejaculation, vaginismus, non-consummation. Is she pregnant?
 Ask about marriage, including number of marriages and type of marriage. Enquire about courtship, the early, middle and late years of marriage, co-operation, sex, budgeting, finances, etc. How does he get on with in-laws? How many children does he have and what is his attitude toward them? Has he had any affairs (be diplomatic)? Ask about parenting, separations, family planning, contraception, abortion, and other forms of foetal and perinatal loss. What are his living arrangements? Is hospitalisation likely to injure his career? Will he lose his accommodation or will it jeopardise his relationships? Who is looking after the children (anyone under age of 18 years according to the Child Care Act 1991)? Who visits him in hospital?⁵⁵
 Has he, or increasingly she, any military experience in the armed forces (combat, injuries, discharge, indiscipline, or symptoms)?
 What does he dream about? Does he daydream or fantasise? What are his main values? Does he, or an informant, know of any 'nervous' problems (get details) among relatives? How has his family and others responded to his present and past episodes? How do they normally react to him?

Mental state examination

'... it is probable that no clinician of the near future will have diagnostic tests for functional psychiatric disorders that are more sensitive than the evidence of his own eyes and ears'. (Fraser, 1990)

Here we are interested in general appearance and behaviour, psychopathology, and *cognition* (processes whereby we identify, understand, retain, and utilise information from outside and within ourselves.).

Organic symptoms and signs

Agnosia: inability to recognise and interpret the significance of sensory perceptions, perception without meaning⁵⁶; can take many forms – *anosognosia*⁵⁷, denial of illness (a form of hemi-inattention; a left hemiparesis is not acknowledged due to a non-dominant parietal lobe lesion⁵⁸; this causes management problems because the patient does not see why he needs assistance; also some such cases are also depressed, which itself may be denied by the patient) – the term *disconnection syndrome*⁵⁹ suggests an interruption of communication between brain regions in sensory inattention and neglect following a stroke⁶⁰; *autotopagnosia*, denial of (failure to recognise/name/point out) body part (one's own or that of

⁵⁵ Contact with relatives may occur for the first time when a discharge date is set, or when the patient is referred from a psychiatric to a general hospital.

⁵⁶ *Gnosis*: ability to recognise objects, faces, sounds, or body parts.

⁵⁷ Gk. *a*, not; *nosos*, knowledge. The term was coined by Babinski in 1914.

⁵⁸ Other authorities point to the right frontal cortex.

⁵⁹ Term coined by Norman Geschwind in 1965.

⁶⁰ Neglect can be **visual**, wherein a clock is drawn with figures bunched to one side or the start of a line or word is not read, or **motor**, as when only one hand is used to carry out a task without any neurological finding by way of explanation. Whilst visual inattention

another person), e.g. finger⁶¹ or own face (as in a mirror: hence the ‘mirror sign’ in Alzheimer’s disease where the patient converses with or is frightened by a ‘stranger’, i.e. his own reflection), despite a retained ability to recognise other objects; *asomatagnosia*, denial of ownership of a paretic limb, sometimes attributing ownership to another person⁶², with a right-sided lesion⁶³; *visual agnosia*, inability to recognise objects visually⁶⁴, mostly attributable to bilateral (less often right-sided only) medial occipitotemporal lesions (ventral stream of visual processing); *auditory agnosia*, inability to recognise sounds, everything from a telephone ringing to speech – all is simply noise (usually bitemporal lesions)⁶⁵; *astereognosis*, inability to recognise objects by touch; *topognosis*, inability to recognise an object placed on the skin; *agraphagnosia (agraphaesthesia)*, inability to recognise numbers or letters written on skin; *prosopagnosia*, inability to recognise familiar faces⁶⁶ (in the extreme case this includes failure to recognise the self in the mirror); *simultagnosia*: inability to recognise more than one element at a time of a visual scene (right temporo-occipital lesion); and, more controversially from the definitional viewpoint, *topographagnosia*, where patients cannot recognise items like buildings⁶⁷.

Alternating sequences: draw a short sequence of alternating squares and triangles and ask patient with frontal lobe pathology to copy the sequence and then continue the pattern⁶⁸; the patient will repeat shapes instead of alternating them.

Attention: the ability to focus in a sustained way on the matter in hand. *Concentration* is the ability to hold that focus. *Latent inhibition* refers to the situation wherein a person becomes used to ignoring a stimulus because of its irrelevance, but when its once again becomes relevant the subject finds it difficult to learn its significance⁶⁹. Terminology around the subject of attention varies somewhat. Krabbendam and Jolles(2002) define attention as a multifactorial construct that includes the capacity to remain alert, orient to new stimuli, to filter what is relevant, and to rapidly discriminate stimuli; sustained attention allows one to be ready to respond to small environmental changes; and sustained attention allows one to focus on the relevant, ignoring the irrelevant. *Sustained attention (vigilance or continuous performance)* is often measured with the *Continuous Performance Test*⁷⁰ (CPT). The *Stroop*⁷¹ *Colour-Word Test* (reading words, naming colours, and an interference condition of names printed in conflicting colours, e.g. ‘BLUE’ written in red)

may be dramatic following an acute cerebral insult the severity of neglect often declines with the passage of time to more subtle levels; the latter may be more obvious during the application of complex stimuli or when a stimulus is simultaneously applied to the unaffected side. The negation of hemi-neglect by the application of transcranial magnetic stimulation to the intact hemisphere (Oliveri et al, 1999) suggests that it is interhemispheric imbalance rather than damage to the other hemisphere that leads to hemi-neglect.

⁶¹ Tests for finger agnosia: recognise/name individual fingers; name finger being touched whilst patient keeps eyes closed. Autotopagnosia is very rare in its full-fledged form. Milder forms may take the form of misidentification of body parts. Most cases involve failure to recognise body parts bilaterally but unilateral cases may accompany unilateral neglect or anosognosia. The pathology in autotopagnosia is usually diffuse. Damage to the left parieto-occipito-temporal is a less common association.

⁶² The term *somatoparaphrenia* is applied to such bizarre beliefs toward a paralysed limb (too many [*pseudopolymelia*], misshapen, not alive, severed, belonging to a named other person [*somatophrenia*], etc). Whether one uses these terms or not depends on whether a psychiatrist is looking for somatic delusions or a neurologist prefers anosognosia. During the 1960s, Sir Aubrey Lewis suggested that lack of insight in schizophrenia was reminiscent of frontal lobe dysfunction and later authors have suggested that there is a parallel with anosognosia.

⁶³ Usually parietal but can be internal capsule, striatum, or thalamus. *Hemisomatognosia* is where there is loss of body image on one side and is found during an epileptic aura or migraine; the person may ignore this part of the body, acting as if it does not exist.

⁶⁴ One may divide **visual agnosias** into *apperceptive* (specific impairments of colour, movement, and form) and *associative* (cannot recognise faces or objects although the patient is sometimes able to copy or match them) subtypes. In contrast to visual agnosia, *deep dyslexia* refers to an ability to read the sense of a word but a word with similar meaning is substituted consciously, e.g. ‘terminal’ for ‘ending’ – a form of adaptation to neural damage.

⁶⁵ **Pure word deafness** is very rare and has been variably classified as an example of aphasia or agnosia. The sufferer hears words as sounds but not as words so that he/she cannot repeat overheard words or write down words that are heard. The lesion is in the dominant temporal lobe near the primary receptive area for hearing.

⁶⁶ Same areas are affected as in visual object agnosia (with which it sometimes occurs); may occur as part of simple partial seizure, when it is of brief duration.

⁶⁷ Alternatively defined as a loss of sense of direction – see ‘geographical disorientation’.

⁶⁸ Alternatively one could ask the patient to connect numbers and letters in the sequence A-1-B-2-C-3-D-4 etc on a page containing randomly situated letters A to G and numbers 1 to 7.

⁶⁹ This phenomenon is lacking to a significant extent in people with schizophrenia. The latter may be less influenced by prior experience, a phenomenon that might have some relevance for the genesis of hallucinations.

⁷⁰ Letters or digits are presented singly in random order and subject must respond when a designated target stimulus appears, although there are variations in practice.

⁷¹ Called after John Ridley Stroop (1897-1973), American psychologist, who described the test during the 1930s.

is often used to assess selective attention. People with left frontal lobe damage perform particularly badly on the Stroop Test.

The related concept of *alertness* has been divided into phasic (a warning stimulus raises the level of attention), divided (ability to attend to more than one stimulus simultaneously and to react to whatever is relevant), and sustained or vigilant (maintaining attention on a task over a long period of time). Whilst focal brain damage may selectively impair one of these subtypes, mixed patterns of different degrees of severity are common.

Buccofacial (oral) apraxia: patient unable to execute the normal facial, lip, and tongue movements, and the problem is not simply due to paresis; severe cases may be almost mute (*aphaemia*⁷²). Broca's aphasia may occur with oral apraxia.

Consciousness: awake and aware; a state of mind which refers to the nature of a person's mental experience at a given moment in time; to be conscious is to be aware of oneself and one's environment; consciousness may be clouded, that is incomplete or diminished; preoccupation may narrow consciousness so that elements foreign to the preoccupation are excluded from consideration; the lay use of consciousness refers to an awareness, e.g. 'I was conscious of your dilemma'. From a biological viewpoint, consciousness is a product of tegmental nuclei of the brainstem reticular activating system; diffuse projections go to the forebrain and diencephalon.

*Dysarthria*⁷³: speech disorder caused by mechanical problems with anatomical structures necessary for articulation of speech. Ask the patient to say 'West Register Street'. Cerebellar speech involves fluctuations in rate, volume and tone, giving the false impression of intoxication. *Anarthria* is the complete absence of speech due to articulation problems.

Dyspraxia (apraxia): absence of praxis without it being explained by diminished motivation, arousal, attention, comprehension of language, or sensorimotor function; *motor dyspraxia* (lesion of dominant premotor frontal cortex or anterior corpus callosum, or diffuse cortical disease) – ask patient to mime simple tasks such as brushing teeth or copy unusual hand postures demonstrated by examiner; *constructional dyspraxia* (especially lesions of non-dominant hemisphere) – inability to construct shapes, by drawing or other means, either on request or when asked to copy a particular design such as a three-dimensional cube, a clock face⁷⁴, or a bicycle; ask patient to light a match (a complex task) to test for ideomotor/ideational dyspraxia (Q.V.). In dressing dyspraxia, the patient has difficulty putting on clothing (e.g. puts on garments backwards or puts arm in wrong sleeve – a good test is to ask a patient to don clothing that has been turned inside-out). Lower limb apraxia is demonstrated by asking a patient to trace specified patterns with the feet on the ground.

Euphoria: unjustified non-infectious happiness, contentment and unconcern; associated with frontal lobe damage or other organic states.

Hypergraphia: uncontrolled excess writing that is correct from a linguistic viewpoint but is nevertheless semantically loose. Causes include CVA, epilepsy, brain tumours, and CJD.

Ideomotor dyspraxia: the patient cannot mime an action (e.g. hair combing, using scissors, or lighting a cigarette) but can carry out the action when given the actual implements (like a comb); in *ideational dyspraxia*, on the other hand, there is defective carrying out of both actions (miming and real).

Logoclonia: spastic repetition of terminal syllable: 'I'm going to the circus, cus, cus, cus.' Found in Parkinson's disease.

*Palilalia*⁷⁵ and *palalogia*: repetition of sounds or words respectively, as distinct from *echolalia*, the repetition of whatever is heard, and *coprolalia*, the uttering of obscenities. See also perseveration.

⁷² *Aphaemia* (or *aphemia*) is also used as a synonym for the very rare **pure word dumbness** (the patient, with a sub-insular lesion, cannot speak normally when he wants to or repeat words overheard or read aloud; he can write; he understands what others say and can understand written material; speech is slurred and poorly articulated). Pure word dumbness is apraxia for spoken speech production.

⁷³ Dysarthria and dysphagia often coexist because of shared neuromuscular control.

⁷⁴ **Clock Drawing Test**: Draw a clock-face with hands indicating a specified time (say 10 past 10 on the 12-hour clock): tests construction, planning and organisation. If spontaneous clock drawing is not satisfactory as the patient to copy one you have drawn – this helps to overcome executive problems such as planning but will be of little assistance to a person with visuoconstruction difficulties.

⁷⁵ However, palilalia is often used to mean repetition of the last uttered word or phrase uttered by *others*. (Sanchez-Ramos, 2004, p. 296) It is also used to mean repetition of *ones own* thoughts or sounds. (Ursano et al., 2008, p. 901) This is a good example of the loose use of terminology in the literature.

Perseveration: same answer is repeatedly given to different questions, or same non-verbal response is given for different stimuli; common in dementia and frontal lobe syndrome; includes palilalia and logoclonia. A patient may never get dressed because he keeps opening buttons each time he closes them or if told to copy an examiner who claps (say a few times) the patient may continue clapping. In perseveration the word or phrase used is initially appropriate but continues to be used though no longer relevant whereas a spontaneous and frequent use of a word or phrase that bears no connection with the circumstances amounts to *verbal stereotypy*.

Reduplicative paramnesia (environmental reduplication): a (variously defined) delusional belief that one is somewhere other than where one objectively is or, whilst incorrectly describing their true locality, patients hold that a familiar place has many copies in different localities, or knows where they are (e.g. hospital) but acts as if they are elsewhere (e.g. home); the actual place where the person is may be novel to that person; described by Pick in 1903; often associated with neurological deficit, e.g. head injury or stroke, especially involving both (or right) frontal lobes. Three subtypes have been described:

(a) **Place reduplication** – 2 identical places exist to which the patient gives the same name, but the places are situated at a distance from one another

(b) **Chimeric assimilation** – 2 places become one, as when a patient believes that home and hospital are one

(c) **Extravagant spatial localisation** – belief that one is in another place⁷⁶, often a place that one is very familiar with

Torpor: state of abnormal drowsiness – patient is sleepy, everything is slowed down⁷⁷, perception is diminished in range, concentration requires great effort, and, unlike in functional stupor, amnesia often occurs following resolution of torpor.

Wada test: inject sodium amytal directly into each carotid artery: when dominant hemisphere is perfused the patient becomes briefly aphasic.

Witzelsucht: silly, loud humour, pranks and punning; indicates organic cause, e.g. frontal lobe disease; *moria* is childish excitement or silliness in frontal lobe disease.

Describe the patient's appearance, including state of dress, posture, and body language. Describe his behaviour, e.g. unable to sit still, aggressiveness, fidgeting, and tics. How does he get on with you? Is he attractive, co-operative, docile, combative, hostile, agitated? Is his speech impaired (stuttering, aphasia, dysarthria), monotonous, fast, absent? Is there any abnormality of content e.g. neologisms? Does he tell you how he feels or does he deny certain feelings without conviction? How deep and sincere are his feelings? Is he calm, euphoric, angry, or frightened? Is his mood constant or fluctuating? Does his culture permit the expression of certain affects?⁷⁸ Does he show a variety of affects or is his affective range constricted? Is his affective expression severely reduced in intensity: blunting - 'flat' if no responses at all? How is the fit between subject matter and affect? Is it appropriate? Does he experience depersonalisation? Does he hallucinate and, if so, in what modality? What are the contents of his hallucinatory experiences, their timing, the 'person' in auditory hallucinations, and is there a temporal relationship with substance use?

Thinking

Slow, hesitant, rapid, full of ideas, bereft of ideas, etc?

Perseveration, loosening of associations,⁷⁹ tangentiality, circumstantiality, evasiveness, rambling?

Distracted by irrelevancies?

Thought block?

Incomprehensible?

Preoccupied?

⁷⁶ Carson et al (2007, p. 341) give as an example the patient who believed that he was being treated in a cruise liner and when he saw hospital porters delivering supplies through his (hospital) window came to the conclusion that the ship was in dry dock!

⁷⁷ Incl. thinking.

⁷⁸ A person's minority culture may lead to misinterpretation of normal distress as psychopathology. **Anger/irritability** may be entirely explicable on the basis of circumstances or it may be abnormal/morbid (out of proportion, pervasive, impulsive, uncontrollable, or occurring with high frequency), e.g. personality disorder, catastrophic reaction in dementia, paranoid disorders, mania (e.g. when thwarted), intoxication, and withdrawal states.

⁷⁹ *Asyndesis*: lack of adequate connection between consecutive thoughts.

Excessively abstract (categorical) or concrete (interprets common metaphors⁸⁰, spot differences⁸¹, or note similarities⁸²)? Recognition of similarities, differences, understand a subtle joke, or recognise an absurd question (e.g. 'Which is the bigger, a square or a circle?')
 Ideas of reference, delusions of persecution, etc.? What are the details, when did they start, what effect have they had, did he act on them or does he plan to do so?
 Effect of current treatment on thinking, behaviour, mood?
 Is his general information in keeping with his job, pastimes, education, background?
 Concentration may be tested throughout the interview and tested formally at this stage, e.g. serial 7's (starting with 100, subtract 7 from each answer⁸³).

What is his level of consciousness (lucid, drowsy, stuporous, and comatose)? Dissociative fugue states, retarded depression, and mute schizophrenia may closely simulate a lowered level of consciousness⁸⁴. Disorientation may be a product of a lack of interest or stimulation (e.g. in institutions), physical treatments, or organic mental disorders; *topographical disorientation*, difficulty in finding ones way even in familiar surroundings, may herald organic brain disease. Approximates are sufficient e.g. the date. In organic disorders the first to go is 'time', then 'place', then 'person' - they improve in the reverse order. How long has he been in hospital, how did he arrive here today, why are you both meeting here, and who or what am I? Inability to name oneself occurs in dissociative states and in advanced dementia, or it can be that the patient is deluded into thinking that he is someone else. Confusion (implying organicity) shows up most in the dark: enquire about its timing/worsening from a relative or nurse.

Memory

Tested throughout the interview
 Direct questions better if related to matters with meaning for the patient, e.g. what happened a few minutes ago, what did he do on his last birthday, who did he marry (maiden name), rather than formal tests such as repeating digits forwards and backwards (e.g. 46932614)
 How does he cope with/hide a poor memory, e.g. notes, diaries, circles on calendar dates?

Judgement may be assessed during the interview or by direct questions, e.g. "If you found a lady's handbag on the street, what would you do?" Alternatively, "If you discovered a stamped, addressed envelope beside a post-box what would you do?"

Does he deny being ill, on has he some strange explanation for his state, e.g. concrete blocking his bowels or a neighbour poisoning him.

How reliable do you think the patient and other informants are in supplying the information you seek, and how motivated is the patient to get better?

Life charts (Sharpe, 1990)

Depict relevant information as it happens chronologically (relapse, remission, life events, treatment)
 Renders correlations immediately appreciable
 Best if prospective

Ending an interview requires that you signal this in plenty of time, e.g. "Since we are nearing the end of the consultation I would like to cover a few areas we may not have touched on." It helps to summarise the main points of the consultation for the patient. This allows him/her to modify emphasis or correct any mistakes. The interviewer then sets out the plan: tests, homework, contacts to be made (and permission given), next appointment, etc.

Formulation/summary

Short version: This is a very brief summary of your knowledge of the case to date, e.g. Mr. J B, a 64-year-old farmer with recurrent memory black-outs over a period of 18 months related to his excessive drinking.

⁸⁰ E.g. 'A rolling stone gathers no moss'. The value of this type of test in detecting organic disease has been questioned because poor abstract thinking is not confined to this group of disorders. Psychotic patients may give revealing interpretations of proverbs.

⁸¹ E.g. 'What is the difference between a mistake and a lie?'

⁸² E.g. 'What have a lake and a bathtub in common?'

⁸³ If the patient finds this to be too difficult they can be asked to subtract 3 serially from 20 (17, 14, etc) or to count backwards from 20 (19, 18, 17, etc).

⁸⁴ **Psychogenic 'coma'** is suggested by normal vital signs (including pupil, corneal, gag, swallow, and oculovestibular reflexes), eyes that stare (rather than wander), and resistance to movement of eyelids/limbs. The EEG may be normal. IV barbiturate may render the patient verbose, unlike the deterioration in attentiveness to be expected with neurological disease.

Long version: This is much shorter than a full history, mental state, diagnosis or differential diagnosis, and plan of action, and contains positive points only, e.g. Mrs. A.H., a 32-year-old housewife from a working-class area in South Treeville presented with a 4-week history of panic attacks, agoraphobia and feelings of depression. Her husband is unemployed, with a history of violence toward Alice whilst he is intoxicated. Reared by elderly parents in rural setting, left school with no exams at 14 years, and went to the city for work. Lost 6 good jobs (range 12 years - 6 days) because of drink problem/absenteeism/poor discipline. Lives on social welfare payments. Outings to pubs only; brings home a bottle of cider. Married age 25 years, first drink age 24 years (with husband). Husband imprisoned twice for assault (6 months, 1.5 years). 3 children (in care - confirmed abuse, non-sexual). Drinks 6 small whiskies and one large bottle of cider daily. Smokes 60 cigarettes per day. Past psychiatric history: in hospital for one day ('drunk'); took own discharge. Past medical history: gastroscopy (normal) last year. Legal: awaiting court proceedings against husband re violation of barring order and non-payment of maintenance. Mental State: actively denies excess alcohol intake, blames problems on marriage. Diagnoses: alcohol - related problems; social problems; ? underlying personality problem. Plan: detoxification, bloods, urinalysis, chest X-ray (?TB), alcoholism counsellor, Alcoholics Anonymous, interview parents (husband unreliable), check with social services re children, discuss case with GP, and ask social worker to interview

A biopsychosocial framework for formulating cases

The doctor considers predisposing (e.g. family history, neglect in childhood), precipitating (e.g. physical injury, divorce), perpetuating (e.g. avoidance, inactivity, long-term unemployment, insomnia, unresolved financial compensation) and protective (e.g. confiding relationship or a hobby) factors under the headings of biology (e.g. genes), psychology (e.g. self-esteem, ability to trust, locus of control) and sociology (e.g. marital status, finances, neighbourhood, legal entanglements), completing the table for the index case.

	Biological	Psychological	Social
Predisposing	-	-	-
Precipitating	-	-	-
Perpetuating	-	-	-
Protective	-	-	-

Symptomatology

'Phenomenology is like a photographic still whilst psychodynamics can be likened to a motion picture.' (Nemiah, 1989)

'No individual symptom is confined uniquely to a single disease...' (Liddle, 2001)

'So many of the terms used in psychiatry are not precise...with different names may partly overlap and coalesce.' (Sims, 2003, p. 221)

For something to be remembered it must be registered (attention, hearing), retained (often unable to do so in early dementia or in Korsakoff's psychosis), and recalled (goes late in dementia - such as maiden name or place of birth).

Amnesia

Amnesia is abnormal forgetting

Common in affective (mood) and organic brain disorders

Recent memory lost first in dementia (*Ribot's law of memory regression*)

Dissociative (may not know own name or address but can learn new information and selectively recall past events; often follows stressful experience) and manipulative 'amnesias' are generally highly selective⁸⁵

Screen memory: consciously tolerable memory serving as cover for an associated memory too emotionally painful to recall – recalls part of true memory⁸⁶ making it difficult for the observer to distinguish what is true – Freud held that memories, particularly those relating to events that happened many years earlier, may be constructed like dreams with elements of self-deception and wish fulfilment

Anterograde amnesia - loss of memory for events following an insult (e.g. cranial trauma)

Retrograde amnesia - not remembering events leading up to the insult

Posttraumatic amnesia - extends from time of injury to restoration of normal continuous memory

Insult may be psychological (e.g. bereavement) or physical (e.g. boxing)

⁸⁵ However, the reader should realise that isolated inability to recall significant personal events (e.g. wedding date) can sometimes be organic in origin and due to brainstem, fronto-basal, or anterior temporal lesions. (Kopelman, 2002) Of course, similar losses may occur as part of dense anterograde memory loss.

⁸⁶ E.g. 'I was attacked by my school mate', when in actuality I was attacked by my mother. Screen memories may be relevant in the debate around 'recovered memories' and the so-called 'false memory syndrome'.

Whilst pure anterograde amnesia is common, retrograde amnesia is almost always accompanied by anterograde amnesia. (Goldstein et al, 2002) Definitions vary between authors. (Kopelman, 1987; Gelder et al, 1996; O'Shea & Condren, 1996)

Retrospective falsification

Patient is unaware that of remembering things in a manner coloured by unconscious factors, e.g. bleak views of the past in depressives (e.g. 'I was always a burden' - mood colours thinking), or wish fulfilment in the jilted ('He didn't say exactly that he would never come back to me!')

Anxiety states may also be accompanied by an enhanced tendency to recall negative or threatening data (Nitschke & Heller, 2002)

In Korsakoff's psychosis, but also sometimes in other organic brain conditions and in schizophrenia (Lorente-Rovira et al, 2007), the patient may *confabulate*, i.e. unconsciously fills in gaps in memory with events that never happened (or, some of these memories may be real but displaced in time). These two distortions of recall come under the heading of *paramnesias*. Some authors divide confabulation into two types: the form occurring when asked about something that one is unable to remember, which might constitute a normal reaction to either a basically poor memory or to a failing memory; and spontaneous confabulation where the patient confabulates freely, a pathological symptom, i.e. a manifestation of an illness process rather than an attempt to cope with a problem. Other paramnesias include *déjà vu*, a subjective feeling of strong intensity that a novel experience was previously experienced, *jamais vu*, a subjective feeling that a previously experienced event is novel, and *déjà entendu*, something which you hear for the first time seems extremely familiar. The last three phenomena are not uncommon in temporal lobe epilepsy (TLE) and are sometimes referred to as *illusions of memory*. *Déjà vu* that lacks the vivid and often clearly repetitive nature of a temporal lobe aura is usually due to anxiety. (Trimble, 1997) *Déjà pense* is a novel thought felt to have occurred previously.

Panoramic recall

The feeling that one is quickly re-enacting long stretches of one's life

Described in TLE

Levels of consciousness may reach extremes of excitation after imbibing LSD25 or an amphetamine. Extreme lowering of consciousness (*coma*) is associated with lack of voluntary movement, absent reflexes, and non-responsiveness to even painful stimuli. Coma due to brain stem lesions may produce alpha or theta coma patterns in the EEG whereas bi-hemispheric disease may produce a delta coma pattern. The term *confusion*⁸⁷, to all intents, is synonymous with disorientation.

In *stupor*⁸⁸, the patient is immobile, mute and unresponsive, but appears to be fully conscious (in neurology the term stupor infers lowered consciousness); he may follow objects with his eyes; if his eyes are closed

⁸⁷ However, it is more complicated than this. Thinking is muddled and disorientation may initially be transient or a patient may be orientated on examination but later be unable to recall the interview. (David, 2009, p. 12)

⁸⁸ The **differential diagnosis of stupor** includes: depression, schizophrenia (one of Bateman's [1990] patients believed that every time he spoke it shortened his life), rarely dissociative states or mania, intra-cerebral (posterior diencephalic and superior midbrain focal lesions such as craniopharyngioma, infarction, meningitis, epilepsy) and extra-cerebral (e.g. uraemia, hypoglycaemia, electrolyte and fluid imbalance, endocrinopathies, alcohol and drug-induced) causes. The EEG may help distinguish organic from psychogenic causes. Disorientation for time is usually an early sign of organic insult (e.g. delirium). The usual site of a lesion in organic cases is upper brain stem or midbrain but it can be in anteromedial frontal lobe or nearby septal area. Cases of hysterical stupor tend to look toward the floor if turned on their side. Stupor from lesions of brainstem is usually accompanied by apathy and sleepiness, and often there is weakness of the extraocular muscles. The patient with stupor due to a frontal lobe lesion - which may involve the anterior cingulate with its subcortical connections) is more often alert and may demonstrate *hyperpathic akinetic mutism* (appearance of vigilant gaze).

Idiopathic recurrent stupor consists of episodes every 1 to 6 weeks during which stupor attacks last 2-120 hours. The patient is only briefly rousable from such a state. Endozepine-4 levels are very high in plasma and CSF. IV flumazenil rapidly normalises the clinical state and the EEG.

he resists attempts to open them; the reflexes are normal; and he can maintain his posture even if he appears to do so clumsily.

Aphasia (Gk. *a*, not; *phasis*, speech): Broca's area⁸⁹ is just below the motor area for the right hand and face. Wernicke's area is in the posterior part of the dominant superior temporal gyrus. The two areas (in most people in the left hemisphere) are joined by the arcuate fasciculus that passes through the angular gyrus. Cerebral dominance⁹⁰ is not well established in very young children. *Dysphasia*⁹¹ (the complete form being *aphasia*) is an organic impairment of language and communication. Broca's aphasia is usually accompanied by contralateral hemiparesis, Wernicke's less commonly so. Wernicke's aphasia is commonly associated with a visual defect, this being rare with Broca's aphasia.

Aphasia

- (a) Receptive (sensory, fluent, jargon) aphasia** - patient hears but *cannot understand* (lesion in Wernicke's area; speech is fluid and spontaneous but incoherent and nonsensical) and is unaware of the problem (may become annoyed or unduly suspicious when not understood); may be mistaken for thought disorder (neologisms, paraphasic errors, and, by way of compensation for communication problems, exaggerated affect); also, impaired naming, repetition, reading, and writing
- (b) Expressive (motor, non-fluent) aphasia** (lesion in Broca's area) - patient understands others but cannot express himself normally: speech is halting, laborious, inaccurate, telegraphic⁹², or even absent - in the lesser, *dysphasic* form the appropriate words cannot be found despite knowing what it is one wants to say (patient may communicate through simple 'yes' or 'no' questions or via facial expression)
- (c) Global (total) aphasia** - combination of (a) and (b) - speech is non-fluent and the patient shows by his emotional reaction that he is unaware that there is a problem
- (d) Conduction aphasia** - similar to sensory/fluent aphasia but with understanding and awareness of deficits, the latter leading to frustration
- (e) Nominal dysphasia (anomia, amnesic aphasia)** - inability to find words or name objects that patient should know (e.g. a pen or a watch) - tested for in detail by asking the patient to (a) name 12 familiar (e.g. a cup) and unfamiliar (e.g. examination couch; teeth of a comb⁹³) objects while he handles each in turn, and (b) name as many members of stated categories (e.g. flowers or animals) as can be recalled

Patients with Broca's dysphasia are frustrated: *emotional speech* is found in such patients: they may utter words or sentences when experiencing great emotion that they would otherwise be unable to produce. The acute onset of abnormal speech in a middle-aged person is almost always diagnostic of a fluent aphasia. (Geschwind, 1971) *Fluent dysphasia* may be misdiagnosed because many doctors are unaware of the frequency of aphasia without a hemiplegia. The patient may be mislabelled as 'psychotic' or 'confused', especially when there is a rapid outpouring of abnormal speech. In practice, the differential diagnosis is not always straightforward.

Nominal dysphasia, unlike primary motor aphasia, may be commoner in diffuse rather than focal brain dysfunction (e.g. Alzheimer's disease), and it is often accompanied by *acalculia* (inability to do simple arithmetical calculations; tested for by 'serial 7s' - this, or *dyscalculia* (*dysarithmetria*: a lesser form, may be acquired or developmental). People with nominal dysphasia are aware of the deficit. A temporary inability to remember a proper noun or name, a universal experience, is called *lethologica*.

Word salad, a mixture of words and phrases lacking comprehensive meaning or logical coherence (lacking grammatical rules; no logical link between adjacent words), is found in schizophrenia.

⁸⁹ Posterior part of inferior frontal gyrus of dominant hemisphere, i.e. Brodmann's (after the German neuroanatomist Korbinus **Brodmann**) areas 44 and 45. Brodmann worked on one brain and since there is great interindividual anatomic variability his 'areas' act only as a rough guide. The contralateral (usually right) area to Broca's area is important in giving emotion to speech in the form of prosody and gestures.

⁹⁰ By this is meant (usually) left-sided dominance for speech. *Cerebral hemispheric asymmetry* is a better term since each hemisphere is dominant/ specialised for/in different functions, e.g. the right side for music.

⁹¹ '...a patient who cannot carry on a simple conversation but who can prepare a full meal likely has an aphasia not a dementia'. (Kelsey ea, 2007, p. 293)

⁹² Sentences shorn to their minimum, e.g. 'Read paper' instead of 'Please read the newspaper for me'.

⁹³ The best words to test for are probably ones that most of us know but use infrequently, e.g. the buckle of a belt, the knuckle of a finger, the dial of a watch, or the sole or heel of a shoe.

A lesion of the angular gyrus leads to loss of ability to read and write (speech, both in terms of production and understanding, is normal), the two kinds of visually mediated language. *Alexia*⁹⁴ is loss of ability to grasp the meaning of written or printed words or sentences. Dyslexia includes word blindness⁹⁵ and a tendency to reverse read or written letters and words. Various acquired alexias⁹⁶ have been described. *Developmental dyslexia* (specific reading retardation) is an isolated problem with learning to read and write. It is not explicable on the basis of IQ or educational opportunity. However, in practice, inadequate schooling and difficult home circumstances may play apart, as may genetic vulnerability⁹⁷. *Agraphia*⁹⁸ is the inability to write and may accompany aphasia or apraxia.

There may be associated neurological deficits in dysphasic patients, e.g. right hemiplegia (Broca's aphasia), hemianaesthesia and hemianopsia (Wernicke's), or all of these (global).

Formal assessment of intelligence in the aphasic is difficult and reliance is placed on non-verbal measures⁹⁹ to obtain an estimate.

Definitions

Praxis (Gk. action) : ability to manipulate body parts correctly in space, i.e. perform a planned complex or skilled motor task.

Engram: a memory trace.

Co-morbidity (dual diagnosis): simultaneous occurrence of two or more psychiatric diagnoses in the same individual. (Kim ea, 2003) There are a number of possible reasons for this common¹⁰⁰ phenomenon: adherence to diagnosis according to operational criteria¹⁰¹; co-occurrence of more than one discrete disorder; one primary disorder with additional secondary disorders; addition of personality disorders to Axis I disorders; intellectual disability; (Timms, 2005) sharing a common biological abnormality; and mental disorders are simply reaction patterns rather than discrete entities, thus allowing for considerable interindividual variability and little consistency. (Van Praag, 1996) Comorbid axes I and II disorders carry a relatively poor prognosis. (Crawford ea, 2008) The term 'dual' diagnosis is often confined to the (common) combination of substance misuse plus a mental illness. (Weaver ea, 2003; MacGabhann ea, 2004)

Formal thought disorder: disorder of the *form* (versus content) of speech; disorganised speech; sometimes divided into positive (extreme incoherence, derailment, tangentiality, illogicality) (Andreasen & Black, 1991) and negative (poverty of production or content of speech) types. Thomas (1995) prefers the term 'communication disorder' to thought disorder. Examples are loosening of associations, flight of ideas, and circumstantiality. Speech which is impoverished of content is spontaneous and of normal quantity, whereas in poverty of (quantity) of speech there is little said.

Incoherence: speech pattern is incomprehensible (synonymous with *word salad*).

Illogicality: speech pattern in which conclusions are reached which do not follow logically.

Effort after meaning: ill person tends to recall events that he imagines caused the disorder rather than giving an objective account of all pertinent details.

Derailment: shifts from one train of thought to another with connection; ideas slip off track onto ideas obliquely related or unrelated to the original ones; seen by some as synonymous with loosening of associations. (Ninan ea, 1998)

⁹⁴ The lesser form is called *dyslexia*.

⁹⁵ In **pure word blindness** (*alexia without agraphia*, the lesion being in left visual cortex plus splenium of cortex callosum) the patient can understand the speech of others but cannot comprehend the written word. Letters can be described and copied but cannot be recognised. Writing, spontaneous or to dictation, is not a problem, but the writer cannot read what he/she has written. Colours are perceived but cannot be named. There is usually a right homonymous hemianopia. In **alexia with agraphia** (*visual asymbolia*) the patient cannot read or write but can use and understand speech; the lesion involves the dominant angular and supramarginal gyri.

⁹⁶ In *deep dyslexia* (vascular lesion centring on right perisylvian region) the patient makes semantic errors, i.e. he misreads words but shows some understanding of the meaning of those words, e.g. 'dog' is read as 'animal'. *Phonological dyslexia* (anterior perisylvian lesion) is an inability to read non-words. In *surface dyslexia* (left insula/putamen lesion) the patient makes regularisation errors, e.g. 'comb' instead of 'come'.

⁹⁷ Loci on chromosomes 6 and 18. (Francks ea, 2002)

⁹⁸ **Pure agraphia** (*agraphia without alexia*) is an inability to write spontaneously or to dictation. The classical lesion is in the second frontal gyrus in front of the hand area but it can be in the parietal lobe.

⁹⁹ E.g. Test of Non-verbal Intelligence -2 (TONI-2). (Sherman ea, 2008, p. 112)

¹⁰⁰ 'Epidemic' according to Escobar. (2005, p. 26)

¹⁰¹ Comorbidity by default. (Van Praag, 1996; Clarkin, 2005) See Tyrer and Silk (2008, p. 6): extensive comorbidity decreases the value of a diagnosis and Comorbidity is more acceptable if it follows from what is known about the index (primary) disorder, e.g. substance misuse secondary to borderline personality disorder.

Miserable mania: elderly manic expresses depressive content in jocular fashion.

Recurrence: new episode of illness after a period of complete recovery; preventive (prophylactic) therapy is indicated.

Relapse: worsening of symptoms after initial improvement in the index episode; continuation treatment is indicated.

Relapse signature: the symptoms shown recurrently by an individual patient in the early stages of relapse.

State dependent learning: relative difficulty in retrieving information or behavioural learning during a different mental state, e.g. something learned when intoxicated can only be recalled when again inebriated, but not when sober.

Talking past the point: patient answers question with inappropriate remark that is obviously incorrect but indicates that he understands the question (Unfortunately, the term is sometimes used to refer to *tangentiality* and *Vorbeireden* is then used as a synonym for talking past the point instead of the approximate answers-type of definition just given).

Transitional object: possession that acts as a comfort in absence of the mother (blanket, doll, etc); associated with Donald Winnicott.

Copropaxia: display of rude gestures.

Ecstasy: rare; extreme well being, usually kept private, without overactivity; may feel in communion with God; found in epilepsy, mania, and schizophrenia.

Elation: increased mood that is infectious to others, as in many cases of mania: ‘infectious jollity’.

Diurnal variation of mood: any variation in mood with a consistent 24 hour cycle (such as worse in the morning and improving as the day progresses) that is independent of environmental events and is the same on all days of the week (e.g. does not change if working or on annual leave).

Pleiotropy: a single cause can lead to a wide range of behaviours; a gene can manifest different phenotypes, as in Marfan’s syndrome.

The rare *foreign accent syndrome* may occur in patients with lesions of the left frontal cortex. A patient, whose speech is otherwise normal, starts to speak with an accent associated with a country to which he or she has no connection.(see, e.g., Seliger ea, 1992) However, *stilted speech*, which may take the form of adoption of a foreign accent, may occur in schizophrenia.

Perception

Mechanism whereby one organises, identifies and confers meaning on ones sensory input (sensation), i.e the bringing of sensory stimuli into awareness

Process of becoming aware of what is presented via sense organs

Perception is modified by cognitive organisation processes and may be attended to or ignored

Body image

Ones sense of the self or body

One definition of an *hallucination* is a that it is a false sensory perception, involving any of the senses, in the absence of a external stimulation of the relevant sensory organ¹⁰². It occurs at the same time as normal perceptions and patients can often distinguish between the two¹⁰³. It has substantiality, is vivid and realistic, appears localised in external space (outside the head, as distinct from the ‘mind’ – an exclusion criterion that this author and many others [e.g. Ninan ea, 1998; Nurcombe & Ebert, 2008, p. 49] do not subscribe to),(Black & Andreasen, 1996) and it arises independently and cannot be conjured up or dismissed.

¹⁰² There is no totally satisfactory definition of a **hallucination**. If pressure is placed on the eyeball and lights are seen there are no lights in the external environment and the relevant sensory organ is being stimulated! Perhaps a better definition refers to the absence of ‘corresponding external stimulus’ or absence of an ‘external source’ (e.g. hearing a voice in the absence of a speaker). Definitions that state ‘in the absence of a(ny) stimulus’ cannot be correct.

¹⁰³ E.g. a person may be able to carry out a conversation with another person despite on-going auditory hallucinations. However, complaints of seeing visions of other people who speak (especially if they converse with the patient) are not likely to reflect hallucinations; rather they are most likely due to lying (malingered or factitious) or a conversion state.(Mullen, 2008, p. 7)

Sims(2003, p. 99) adds that the hallucinator often does not believe that other people can share his experience and a 'delusional explanation may be given for this'. Patients often do not seem to care if they cannot explain whence or from whom hallucinations arise. One patient with borderline personality disorder claimed to be able to see 'little green men' outside in the garden every time she raised the window blind! Hallucinations would be expected to be present no matter whether the blind was raised or lowered.

Likewise, if a patient destroyed his tympanic membranes it should not eliminate auditory hallucinations. Cocainism is often associated with *haptic* (tactile) sensations of insects crawling beneath the skin ('cocaine bug'). *Somatic hallucinations* are sometimes divided into *superficial* (haptic: touching, tickling; kinaesthetic: movement, joint position; thermic: hot or cold; hygric: wetness) and *deep* (visceral changes, sexual stimulation, electricity passing through the body) subtypes. *Visual hallucinations* (incl. autoscopic) are due to organic pathology or drugs until proven otherwise. However, they may also be found in schizophrenia, severe affective disorder, following torture (Rasmussen, 1990) and, in 12% of cases in one series, in 'hysteria', (Perley & Guze, 1962) which today would be called dissociative disorder. They may also occur in people with eye disease (Charles Bonnet syndrome). Anticholinergic drugs may be associated with visions of bugs crawling on the skin. Olfactory hallucinations may, for example, herald an attack of TLE, the ictus commencing in the uncus ('uncinate fit'). Gustatory (taste) hallucinations should not be confused with the various tastes produced by drugs.

Pseudohallucinations, an imprecise and controversial term that would be better discarded according to some authors,(Taylor, 1981) involve the reporting of hallucination-like experiences but without an identifiable percept: he may see things that are not there but is unable to describe an actual specific perception; they are less vivid and realistic than hallucinations, are often located inside the head (internal space), and often coincide with true hallucinations¹⁰⁴. These 'as if' experiences are not necessarily abnormal. However, the present author agrees with Owens et al (2004, p. 234) when they say that hallucinations arising from within the head are true hallucinations, there being nothing 'pseudo' about them. Schweitzer and Parker (2007, p. 179) point out that auditory hallucinations in psychotic depression are 'located inside the head' but then weaken the argument somewhat by adding that they may be interpreted as 'voices of conscience'. In addition, Kapur and Mamo (2004, p. 119) state that, depending on the salience attributed to the internal perception, a person might experience an auditory hallucination varying from hearing his own thoughts within his head 'all the way through' numerous external voices commenting on the hearer's activities. Mullen (2008, p. 9) states that pseudohallucinations are as real (and abnormal) as hallucinations.

Far more common in psychiatric practice are *illusions* (distortion or false judgement of a perception of a real object; 'the food tastes queer' - may progress to a delusion of poisoning) of taste. It should be remembered that visual hallucinations due to disease of the central pathways of the visual apparatus are rare. *Hypnagogic* (going to sleep¹⁰⁵) and *hypnopompic* hallucinations (on waking) occur when the level of consciousness is between waking and sleep, and they are often normal.

Lilliputian or microptic hallucination

Bright, funny, everything is much reduced in size

Aetiology:

Alcohol

Anaesthetics

Enteric fever

Scarlatina

Delirium tremens - small, obscene and abusive creatures (Sims, 2003, p. 45)

Micropsia and macropsia

Seeing things as smaller or larger than they should be

¹⁰⁴ Philpott (1997, p. 294) says that patients recognise these pseudohallucinations as imaginary and he includes seeing/hearing/feeling a lost loved one in the definition.

¹⁰⁵ Many people have a problem remembering which of these two phenomena occur when going to sleep versus on waking from sleep: the clue is in *hypnagogic*, i.e. the go = *going* (to sleep).

Aetiology:

Some cases of panic disorder (Coyle & Serman, 1986)

Schizophrenia - demonic or religious visions, small people, or distorted facial features (Salo & Robertson, 2003, pp. 493-5)

Micropsia, macropsia, and *dysmegalopsia*¹⁰⁶ can also occur with organic states or epilepsy

*Alice in Wonderland syndrome*¹⁰⁷ is associated with migraine, hallucinogen use, seizures, viral encephalitis (esp. Epstein-Barr virus) and lesions of the non-dominant parietal area

A *reflex* hallucination occurs when one sensory modality is excited and the cause is irritation in another, e.g. dental caries causing a noise to be heard. As such it is a synaesthetic phenomenon.

A *functional* hallucination is provoked by a stimulus and occurs in the same sensory modality as the stimulus; both the stimulus and hallucination are perceived at the same time and are also perceived as being distinct. A classical example would be when a person turns on a tap and only hears a hallucinatory voice whilst the water is running, but he also hears the water running.

Unfortunately, some authors (e.g. Cutting, 2003, p. 16) view reflex and functional hallucinations as being synonymous and define it as per the above definition of functional hallucination.

Auditory hallucinations, like those in other sensory spheres, need not be well formed. *Crude* hallucinations include buzzing noises and spots of light.

Auditory hallucinations are commonest in schizophrenia and in alcoholic hallucinosis. (Cutting, 1989) They sometimes occur in depression, mania, or after damage to one of the temporal lobes, and, very rarely, they are a manipulative or hysterical symptom. They may occur as a transient phenomenon in normal people.

Just over 50% of schizophrenic patients hear voices¹⁰⁸ at sometime. In alcoholic hallucinosis the voices respond poorly to neuroleptics but they clear if the patient remains abstinent. Normal people may hear noises or voices when dropping off to sleep, on waking, when tired, when exposed to extreme sensory or social isolation, or at the height of a bereavement - the voice may simply call the person by name, e.g. 'Jack!' Defective hearing aids may account for some cases of auditory hallucinations, or the hearing of additional hallucinations in those who already hallucinate. (King, ea, 1989). There is evidence from fMRI that hallucinating schizophrenic patients activate cortical regions mediating the generation of inner speech before areas implicated in the perception of sounds become engaged. (Shergill ea, 2004) However, the match between inner speech and hallucinatory phenomenology has been challenged by Langdon ea (2009) who also found little difference between the inner speech of hallucinating schizophrenic patients (N = 29) and healthy controls (N = 42); the study involved asking the participants questions about hallucinations and inner speech and the authors pointed out that thought disorder was not a marked feature of the ill group.

Extracampine hallucinations are visual hallucinations seen outside the field of vision, such as behind oneself, or auditory hallucinations reported to be heard from outside the range of unaided hearing (e.g. from another country or town). They may occur in normal people as a hypnagogic phenomenon¹⁰⁹, in schizophrenia, or in organic disorders including epilepsy. (Sims, 2003, p. 112)

Autoscopy (phantom mirror image)

Seeing a vision of oneself outside oneself, usually to the front

Can occur with organic (e.g. simple partial seizures or delirium or migraine) and functional states (e.g. schizophrenia)

¹⁰⁶ Objects seem larger on one side than the other when in fact they are of equal size. *Metamorphosis* means that objects appear irregular in shape when in fact they are not; retinal scars can cause this or macropsia whereas an oedematous retina can be associated with micropsia. *Porropsia* means that objects may seem to retreat into the distance (overlap with micropsia).

¹⁰⁷ Distorted perception of objects, usually microptic or macroptic, distorted time sense, and visual hallucinations.

¹⁰⁸ The word *phoneme* is sometimes used to indicate an hallucinatory voice but it is more often refers to constituent speech sounds.

¹⁰⁹ In a community study covering a wide age range (Ohayon ea, 1996) 37% and 12.5% of people reported experiencing hypnagogic and hypnopompic hallucinations respectively.

Can occur transiently as a normal phenomenon if the person is fearful, tired, intoxicated, suffering from sensory deprivation (out-of-body experience), or as hypnopompic or hypnagogic hallucinations¹¹⁰
 Occasionally it may be encountered in the context of organic brain disease, as in temporal lobe epilepsy
Negative autoscopy is not seeing ones reflection in the mirror
Internal autoscopy is a rare phenomenon where someone sees their own internal organs which they describe in a naive manner
Mirror sign - seen in dementia: non-recognition of ones image in a mirror¹¹¹

Autoscopy is reminiscent of the *doppelganger phenomenon*: a direct encounter with the self is experienced, either in the form of a hallucination or an illusion, and the perceived figure shares the same personality and identity as the self.

Olfactory hallucinations occur in depression¹¹², schizophrenia¹¹³, *olfactory reference syndrome*, and temporal lobe epilepsy¹¹⁴. (Meats, 1988).

Olfactory reference syndrome (ORS - Videbech, 1966)¹¹⁵

Usually a true olfactory hallucination

Believed by patient to arise from the self

No prior depression of mood

Excessive washing of hands, changes of clothing, and avoidance of other people

Associated with delusional disorder

Fish odour syndrome (trimethylaminuria) (Humbert ea, 1970¹¹⁶; Mitchell & Smith, 2001)

Example of a non-hallucinatory disorder – fishy smell from patient leading to social ostracism

Rare (F > M) metabolic disorder, usually autosomal recessive

Mutations of FMO3 gene¹¹⁷ on chromosome 1q with defect in FMO3 production

Unable to break down trimethylamine (TMA) properly leading to its accumulation

TMA appears in body fluids (sweat, urine, breath, vaginal secretions)

Exacerbated premenstrually, by oral contraceptive pill, and around menopause

Diagnosis: urine TMA/TMA oxide ratio

Avoid eggs, legumes, some meats, fish and foods containing choline, carnitine, nitrogen, and sulphur

Olfaction in psychiatry (O’Shea & Haque, 2004; O’Neill & Regan, 2004; Sawa & Cascella, 2009):¹¹⁸ When testing the sense of smell, not that ammonia and alcohol may stimulate the fifth cranial nerve and the resulting reaction may lead to confusion in the examiner! Also, avoid esoteric odours like cloves. Instead, coffee, wintergreen, or peppermint are useful. Olfactory problems may operate in a variety of disorders, such as Alzheimer’s disease, Parkinson’s disease¹¹⁹, dementia with Lewy bodies, Korsakoff’s psychosis,

¹¹⁰ It can also be part of a near-death experience. A rare complication is the Doppelganger phenomenon where the person also believes that they have a double.

¹¹¹ The patient may have a conversation with the reflection or ask it to ‘leave’ the house! The *TV sign* is when the viewer believes that characters on the television screen are actually present in the room. Perhaps because of non-recognition of family, a person may believe that other people live in his/her house: *phantom boarder syndrome*. Prosopagnosia in its severest form may include failure to recognise ones reflection in the mirror. However, this is most commonly found in dementia with its more global manifestations. Rarely, a patient may look in the mirror and decide that the reflection represents an untrue version of the self (shades of Capgras, although the patient may simply be unsure of the facts).

¹¹² Usually a foul odour; two-thirds believe that they are the source of the odour; seldom associated with other sensory abnormalities; usually an endogenous depression with retardation, depressed mood, and morbid thoughts.

¹¹³ Common but usually subordinate to hallucinations in other modalities; may be dominant in late-onset paranoid cases; believes smells are being forced on him and may take action to stop it, e.g. blocking up the chimneys.

¹¹⁴ Almost always recognised as a subsidiary part of the illness by the patient.

¹¹⁵ See also delusions of bromosis which Munro(1999) views as synonymous with ORS.

¹¹⁶ The condition is probably ancient. Shakespeare’s Caliban, an outcast in the *Tempest*, appears to have had this syndrome. It is also known as fish malodour syndrome.

¹¹⁷ The enzyme flavin-containing monooxygenase-3.

¹¹⁸ According to Schiffer and Lajara-Nanson,(2003, p. 16) smoking may be the major cause of impaired olfaction in the Western World.

¹¹⁹ Between 70-90% of Parkinson’s disease sufferers may have poor sense of smell and this may precede motor phenomena. It is often not recognised by the patient.(Henderson ea, 2003)

schizophrenia¹²⁰ (close relatives lying between patients and controls: Sawa & Cascella, 2009), Huntington's disease, Down's syndrome, and depression (Harrison and Pearson, 1989; Scalco ea, 2008) as well as PTSD.(Dileo ea, 2008) Compton and Chien (2008) failed to find a correlation between schizotypy based on the *Schizotypal Personality Questionnaire* (Raine, 1991) in healthy first-degree relatives of people with schizophrenia and related disorders and olfactory ability as measured by the *Pennsylvania Smell Identification Test*.(Duty ea, 1984) Turetsky and Moberg (2009) used two fruity/floral odorants (citralva and lylal) that differ in their relative activations of cyclic AMP (which mediates signal transduction in olfactory receptor neurones) and found that schizophrenia patients and their well first-degree relatives, but not comparison subjects, were unable to detect differences between the two odorants. The anterior olfactory nucleus in Alzheimer's disease contains senile plaques, neurofibrillary tangles and reduced cell counts, and the olfactory bulb also shows involvement, as does the nasal sensory epithelium.(Talamo, ea, 1989) Odour detection, odour identification, and odour memory/recall are affected differently in different disorders. Omega-3 fatty acids¹²¹, S-adenosylmethionine (SAME¹²²), and combinations of inositol and lecithin cause gastrointestinal distress and a fishy odour.

Complexity of hallucinations: Hallucinations can be amorphous, elementary (e.g. simple noises or 'seeing stars') or complex (e.g. hearing voices, or experiencing a panoramic vision).

Pareidolia

Normal phenomenon of conjuring up images when looking at ill-defined impressions like the child who likes to see soldiers on campaign when resting in bed (his flexed knee becomes a mountain, etc) or the adult who 'sees' things in the cooling hearth or a pattern in wallpaper or carpet

Affect illusion

Misinterpretation of vague or ambiguous stimuli during a state of strong emotion as representing a threat, as when a criminal is 'seen' in dimly lit, windblown bushes

Eidetic imagery

Resembles 'visual memory': I see the page before me and can read verbatim' - common in children or with hallucinogen use

After images

Persistence of retinal impressions; stare at a simple design on a white page for a while and then look away – you will still see the design

Palinopsia

A visual image remains, usually for several minutes, after removal of the object because of a non-dominant parieto-occipital lesion (an evolving hemianopic visual defect may be found; there may be distortion of object shape and size)

May occur as a manifestation of simple partial seizures (Muller ea, 1995) or, rarely, trazodone (Good, 2000)

Trailing phenomenon

¹²⁰ Changes in markers indicating abnormal development/differentiation of neurones were reported in olfactory epithelium in schizophrenia.(see Sawa & Cascella, 2009) A report of relatively shallow olfactory sulcus in schizophrenia might indicate early disruption of embryonic development.(Turetsky ea, 2009)

¹²¹ Mainly found in oily fish, e.g. mackerel, salmon, herring, and sardines. They have been shown to help with secondary prevention of cardiovascular disease.

¹²² Popular over-the-counter antidepressant that is involved in transmethylation reactions and may increase 5-HT, noradrenaline and dopamine availability. SAME levels depend on B12 and folate levels. SAME may cause anxiety/agitation/insomnia, anorexia/dry mouth,bowel problems, palpitations/dizziness, headache, and sweating.

Perceptual abnormality associated with hallucinogens or nefazodone (Good, 2000) wherein moving objects are seen as a series of discrete and discontinuous images

It has been claimed that monaural occlusion using an earplug leads to improvement in hallucinosis in schizophrenia. Hallucinations may occasionally have an hysterical basis.(Andrade & Srinath, 1986) One theory holds that auditory hallucinations represent verbal activity originating in the non-dominant cerebral hemisphere. The dominant hemisphere then views this activity as alien to the self because of a primary dissociation in the functioning of the two cerebral hemispheres in schizophrenia.(Green ea, 1983) In 1897, Parish conjectured that patients who report hallucinations concurrently generate *automatic speech*. Hallucinations may be seen as an expression of brain activity or as products of adaptive behaviour, as when seeking organisation in a chaotic array or motivated by dynamic imperatives. These views are not mutually exclusive. In particular, thought-disordered content could be superimposed on either primary or compensatory brain-based phenomena. During simultaneous occurrence of hallucinations and external stimuli, hallucinations were reported to lower N100 amplitudes and changed topography, suggesting competition between auditory stimuli and hallucinations for physiological resources in the primary auditory cortex; auditory hallucinations may therefore be a consequence of abnormal primary cortex activation.(Hubl ea, 2007) *Subvocalisation* could either accompany hallucinated voices or generate them. Interestingly, subvocalising during reading decreases reading speed but improves comprehension.(Judd, 1927) Lindsley (1963) took the vocalisations of hallucinations to be the patient's response to the hallucination. Bick and Kinsbourne (1987) found that schizophrenic patients reported that the voices they heard went away when they kept their mouths open, so precluding subvocalisation, but not when they merely clenched their fists. They suggested that hallucinations might be projections of the schizophrenic patient's verbal thoughts, subvocalised due to deficient cerebral cortical inhibition. Nevertheless, most patients with schizophrenia can make clear distinctions between auditory verbal hallucinations ('voices') and their everyday thoughts¹²³.(Hoffman ea, 2008) Nevertheless, patients with schizophrenia may be biased in such interpretations toward false positives.(Vercammen ea, 2008) The box contains important definitions.¹²⁴

Definitions

Lability of affect: variably defined as excessive emotional responsivity or unpredictable changes in affect, such as when the happy person suddenly becomes angry, only to sink into despair a short time later (e.g. in multiple sclerosis and other organic disorders, arteriosclerosis, hypomania, maternal blues); extreme cases reach *involuntary emotional expressive disorder (IEED, pseudobulbar affect, emotional incontinence)*; in pseudobulbar palsy (dysphagia, dysarthria, emotional incontinence, and brisk jaw jerk), bilateral upper motor neurone lesions cause dysfunction of the bulbar musculature, often with emotional lability. Drugs used to treat IEED include amitriptyline, fluoxetine, and levodopa. Winston Churchill told his doctor on July 3, 1953 that 'Since this (stroke) happened I have been very lachrymose. At parts of Phineas Finn I became very tearful, though it is not at all a moving story'.(Moran, 1966)

Incongruity (inappropriateness) of affect (parathymia): common in schizophrenia, e.g. outburst of fatuous giggling or smiling when telling bad news or a strong or weak reaction to unimportant or normally catastrophic news respectively; embarrassment or simple anxiety may mimic this phenomenon and should be outruled before making such a serious observation. In schizophrenia, the emotional reaction may initially be congruous but then not change with altered circumstances, so-called *stiffening of affect*.

Abulia (Gk. *a*, not; *boulē*, will): lack of will or motivation¹²⁵ (often unable to make decisions or set goals); *avolition* is an inability to initiate and sustain goal-directed voluntary activity. The patient with *abulia* has no impulse to action, his mind is blank and empty, and volition is absent. He sits about doing naught. Boredom is not causative. If pushed or supervised he is capable of doing much more. It is classically associated with schizophrenia. However, it has also been described in association with damage to the

¹²³ They do this by examining mainly thought content and sense of control, whereas loudness and clarity are of lesser use.

¹²⁴ In reading these, one should recall Kendell's (1993) words: 'The existence of a number of alternative definitions also helps to emphasise that all definitions are arbitrary, justified only by their usefulness, and liable to be altered or supplanted'.(see also Pawar & Spence, 2003)

¹²⁵ **Motivation** (Latin: *movere*, move): internal (e.g. hunger or curiosity) and/or external (e.g. exams or money) prods to act.

intralaminar thalamic nuclei, the basal frontal cortex, and, as may follow CO poisoning, damage to the basal ganglia. Tumours causing abulia are most often found to affect the frontal lobes.

Apathy with blunting or flattening of affect may also occur in schizophrenia; also common in dementia and after stroke. In one study of stroke (Brodaty ea, 2005) apathy was present in 26.7% of cases compared to 4.5% of controls. There is said to be sustained emotional indifference or diminution of emotional response, although a flat affect is quite compatible with subjective emotional arousal. Should only be diagnosed when subject has been observed in a variety of circumstances and when not sedated. Should be distinguished from culturally restricted emotional display. Flattening of affect can accompany frontal lobe lesions as part of an apathetic-akinetic syndrome. Apathy in neuropsychiatric illness has been treated with amphetamine, methylphenidate, selegiline¹²⁶, bromocriptine, rivastigmine, amantadine, and bupropion (bromocriptine and amantadine are most often used for Parkinson's disease rather than for drug-induced EPSE, and they carry a risk of exacerbating psychosis). SSRIs may cause apathy. (Price ea, 2009)

Fear is induced by an obvious threat, e.g. a charging bull.

Anxiety is characterised by apprehensiveness and tension, but the stimulus is ill defined and may be totally intrapsychic, e.g. a fear of harming one's mother may lead to anxiety. *Free-floating anxiety* has no object. When anxiety is attached to an object it is termed a phobia. *Signal anxiety* alerts us to do something that is necessary, e.g. study for exams; it helps us to mobilise defences early on during a traumatic experience, thus attenuating the emotional impact. It has been suggested by many authors that anxiety disorders properly belong with the affective disorders.

Phobias (simple, social, agoraphobic): patient recognises their irrationality; they persist despite rational argument; and they lead to avoidance of what is feared.

Panic: a state of overwhelming anxiety.

Depersonalisation: feelings of weird and inexplicable change in self ('I feel strange, dead, hollow, like a puppet, etc. '); subject may feel as if he is outside his own body looking at himself. *Derealisation*: similar notions about the external environment (things are bigger or smaller, closer or further away, two-dimensional, flat). Both states are common in severe anxiety from any cause and do not of necessity indicate that the patient is ill – it is very difficult for someone to describe an unpleasant state of loss of normal emotional responsiveness; causes include normal emotional upset, tension or fatigue; a symptom of psychiatric or physical illness; and primary cases, the so-called 'depersonalisation disorder'. Depersonalisation and derealisation are common during adolescence.

Ambivalence: mixed feelings or opposing impulses experienced about something or someone experienced simultaneously.

Flight into mania: Freudian idea that mania was a defence against depression - manics do lapse transiently into tears all of a sudden, and there true 'mixed states' (e.g. co-mingled mania and depression). The patient who finds out that he has a month to live and who then goes around with a smile on his face and joins the local football team might be using the defence mechanism called *reaction formation* (doing the opposite to what one might expect like crying, feeling depressed, looking for a second opinion, preoccupied, etc).

Paradoxical reactions are also found in some people on disinhibiting drugs, e.g. rage with diazepam.

*Obsessions*¹²⁷: persistent thoughts (including mental pictures or images) or impulses experienced as unwanted and ridiculous but which the patient is unable to resist; perceived as senseless, or at least as senselessly insistent; obsessions appear to be common in adolescence (Crye ea, 2010) and are not necessarily abnormal at that stage.

Compulsions: acts, such as rituals, resulting from obsessions. *Obsessive-compulsive disorder* (OCD) is characterised by obsessions and compulsions and may occur in the absence of any other psychiatric disorder. *Obsessional thoughts* consist of words, beliefs, ideas or images that the subject recognises as his own but that intrude forcibly into consciousness, are usually distasteful, and the subject tries to exclude them. *Obsessional ruminations* consist of an argument going on in the mind in which the pros and cons are gone over *ad infinitum*. In *obsessional doubting* the subject worries lest he has failed to complete some action, done harm, or told the priest all his sins in the confessional (scrupulosity). *Obsessional impulses* urge the patient to perform acts, often of a violent or socially embarrassing variety. *Obsessional rituals* are either repetitive, meaningless acts or some mental activity like repetitive counting e.g. touching the corners

¹²⁶ Selegiline may cause mania and psychosis, possibly because its metabolites include L-amphetamine and L-methamphetamine.

¹²⁷ L. *obsidere*, to besiege.

of a desk an even number of times. *Obsessional phobia* is a misnomer and not a true phobia; e.g. a subject with an urge to shoot someone avoids firearms. *Obsessional slowness* (uncommon) involves extreme slowness of ordinary activity. It should be noted that obsessional rituals may raise or lower anxiety levels in different instances. While some individuals with OCD have obsessional personalities, the latter are more likely to develop depression.

Psychomotor retardation: slowing or sluggish thinking and movement; common in depression. Agitation and retardation may coexist.

*Automatism*¹²⁸: repetitious, mechanical and seemingly undirected activity seen in, e.g. conversion states or an epileptic fugue.

Negativistic behaviour: associated with naughty children and schizophrenia; patient does the opposite of what is asked for no apparent reason, e.g. he takes his hand away from you when you try to shake it; patient appears to be uncooperative.

Echolia: automatic repetition of another person's spoken words. *Echopraxia*: automatic repetition of another person's actions. These two phenomena occur in schizophrenia, organic brain damage, and Tourette disorder. Catatonic patients may reply to a question by echoing the content of the question but using different words, so-called *echologia*.

Stereotypy: an action, or group of actions, or words monotonously repeated (see and contrast with perseveration), or a posture maintained long after tiredness would normally have forced the person to quit; non-goal-directed, e.g. rocking, grimacing; *Schnauzkampf* refers to stereotypy seen in catatonia when the lips are thrust forward like an animal's snout (frozen pout).

Mannerisms: repeated, usually odd, goal-directed movements (e.g. eating, flicking dust from the table) or unusual postures; differ from stereotypy by being more in keeping with the personality and by not being repeated so monotonously; found in schizophrenia, intellectual disability, and normals.

Tic: involuntary, sudden, rapid, recurrent, non-rhythmic stereotyped motor movements or vocalisations; can be *simple* like blinking or *complex* such as smelling or jumping.

Verbal mannerisms: Repeated odd use of language short of thought disorder.

Narcoleptic syndrome: narcolepsy, Hypnagogic hallucinations, *sleep paralysis* (frightening - cannot move for a minute or so on waking or going to sleep or coming out of a nap), and *cataplexy* (sudden, transient loss of muscle tone and muscular weakness, often brought on by heightened emotion, e.g. 'my necks gets weak when I laugh').

Catalepsy: increased muscle tone and rigid posture; may occur in schizophrenia, 'hysteria' or organic disorders¹²⁹.

Waxy flexibility (flexibilitas cerea): found in catatonic schizophrenia, stuporose type: resistance to passive limb movement resembling that found on bending candles of olden days; a limb left in any position will remain there despite gravity (as when a patient does not lower the arm after the doctor has finished taking the radial pulse).

Form of thinking may be *concrete* (literal interpretation of everything, including proverbs: found in normal children, organic brain syndromes, schizophrenia, and intellectual disability), *abstract* (ability to formulate concepts and to generalise from the particular, as in normal adults – *categorical attitude* refers to abstract attitude: the ability to shift readily from concrete to abstract as needed), *dereistic* (silly - typically found in schizophrenia), *autistic* (inner fantasies dominate¹³⁰), or *over-inclusive* (full of irrelevancies). Proverb interpretation might be tested thus: 'Tell me how you would explain the saying 'Don't cry over spilled milk' to a young child'. Proverb interpretation is closely related to academic achievement and level of acculturation and a better test is to ask about similarities and differences between objects.

Dysprosody (aprosodia [Gk. *a*, not; *prosodia*, modulation of voice]: *prosody* is that part of speech that conveys mood/shades of feeling): inability to change intonation of speech in order to convey feeling – speech lacks stresses, pauses, accent, cadence, accent, intonation, emotion and melody, being flat, lifeless and monotonous (*expressive aprosodia*). There may be difficulty in appreciation the emotional tone of another person's speech (*receptive aprosodia*). A non-dominant lobe dysfunction – may follow a stroke

¹²⁸ **Legal automatism** are divided into internal ('insane' – arise from internal factors) and external ('sane'). *R v Burgess* in 1991 created difficulties in relation to classification. It was argued that somnambulism was genetic (internal, arising from a certain sleep stage) and therefore carried a risk of recurrence. However, some countries regard somnambulism as causing external automatism.

¹²⁹ E.g. encephalitis, vasculopathies, and mid-brain neoplasms.

¹³⁰ *Autism*, from Gk. for 'self'.

affecting right frontal and temporo-parietal regions¹³¹. May mask underlying depression (Dubovsky, 1986) or may simulate depression. To examine prosody stand behind the patient (so he cannot see your face) and say 'I'm going to leave now' in neutral, sad, happy, and angry tones. Ask the patient to identify the emotion (sad, etc) attached to each statement. Then ask the patient to reproduce these four feelings whilst saying the same sentence. One should, of course, normally be on the lookout for disordered prosody during the interview.

Logorrhoea: copious coherent and logical speech.

Apperception: perception modified by emotion, memory or bias; from a cognitive theorist's viewpoint this includes all perception! On the other hand, *syntactic mode* refers to a mode of perception that forms whole, coherent pictures of reality that can be validated by others.

Alogia: from Greek for 'without speech'; impoverished thinking, often seen with schizophrenia; includes poverty of speech or of speech (thought) content, thought blocking, and increased latency (long delay before replying) of speech; coined by Kleist in 1930 (trans. 1987) to indicate failure in the process of thinking.

Amimia: a language disorder in which there is an inability to make gestures or understand their significance, e.g. shoulder shrugging. *Hypomimia* (reduced facial expression, mask-like facies) is associated with Parkinsonism.

Pressure of speech: cannot stop talking; speech is rapid and difficult to interrupt; increased amount of speech; found in mania.

Prolivity: mild (verbosity, rapidity, and difficult to follow) or 'ordered' flight of ideas; found in hypomania; embellished lively speech with some difficulty maintaining thread of thinking.

Distractibility: distracted by nearby stimuli that interrupt flow of speech; relatively unable to inhibit responding to irrelevancies; unable to facilitate goal-directed responses. The Stroop Colour-Word Test assesses distractibility.

Some patients find it very difficult to get to the point: *circumstantiality* - keeps going off the point but gets there eventually - follows a very indirect and delayed path - found in intellectual disability, obsessional people, and, historically, epilepsy; *tangentiality* - never quite makes the point: the patient replies to a question in an oblique or irrelevant manner; in *asyndetic thinking* language retains intact grammar but thoughts appear completely unconnected - this is basically severe tangentiality; if tangentiality is accompanied by pressure of speech we have flight of ideas.

Flight of ideas: found in mania, some excited schizophrenics, and organic disorders such as disease of the hypothalamus - rapid, loosely connected, rhyming, punning, and clang associations; incoherence found in severe cases.

Clanging: sound of a word rather than its meaning determines direction of talk; some connection between sentences remains discernible in mania - all connection may be lost in schizophrenia. E.g. response to 'I'm a conservative' becomes 'Preservatives are important'!

Cluttering: rapid, erratic speech with disturbed fluency that is difficult to comprehend; found in childhood.

Overinclusion: irrelevant thoughts contaminate speech, e.g. in schizophrenia.

Knight's move thinking: a characteristic of schizophrenic thought disorder; essential step omitted in reasoning process.

Neologism: idiosyncratic word that only means something to the speaker and is unintelligible to the listener; frequently a condensation of different words; found especially in schizophrenia¹³² but also seen in Wernicke's (sensory/receptive) aphasia¹³³. When neologisms occur close together, as in the above sample, we speak of *word salad* (mixture of words and phrases lacking comprehensive meaning or logical coherence, i.e. *incoherence*). When all speech is neologistic we might use the old term *schizophasia*.

Verbigeration, again characteristic of schizophrenia, consists of constant repetition of nonsensical words or phrases, or of sensible words and phrases used repetitiously and nonsensically.¹³⁴ *Glossolalia* is gibberish-like speech or 'speaking in tongues'; may be normal if part of accepted religious practice.

¹³¹ Corresponding to speech expression and reception areas of the dominant hemisphere.

¹³² E.g. 'I glabbed a spurious latyx and poured out a glibrill!'

¹³³ In receptive aphasia, apart from use of neologisms, words are employed incorrectly, there are paraphasic errors (tendency to use ordinary words in unusual ways), and there are problems with syntax and grammar.

¹³⁴ Terminological use unfortunately varies with source, e.g. there is a modern tendency to use the term word salad to refer to the *most extreme form of senseless speech*.

Paraphasias or *metonyms*: the schizophrenic tendency to use ordinary words in unusual ways. The schizophrenic may repeat certain *stock words* and employ them idiosyncratically. There is obviously overlap in the usage of these various terms. Damage to Broca's area causes *phonemic* paraphasia with a change in the word's sound as, e.g., electricrery for electricity. Perisylvian pathology gives rise to *semantic* paraphasia with substitution of one word for a related word, e.g. orange for apple. In semantic dementia¹³⁵ the patient may give a wide superordinate response, e.g. 'clothes' when shown a hat.

Thought block: schizophrenic patient's speech is suddenly interrupted/comes to a halt; he then goes on talking about something else after so many seconds; patient may complain that his/her mind is empty during discrete periods; unable to recover what has just been said; rare¹³⁶; differentiate from fatigue, preoccupation, anxiety/stress, depression (retarded speech), amphetamine intoxication, interference from auditory hallucinations, the normal experience of one's train of thought being suddenly interrupted by another by asking the patient for detail, and absence in petit mal epilepsy. In other words, thought blocking should only count toward a diagnosis of schizophrenic thought disorder if there is other evidence to back up such a conclusion. (Mullen, 2008, p. 34)

Mutism: nothing is said; found in, e.g., depressed or catatonic schizophrenia; mixed mutism and excitement can occur (e.g. running or dancing whilst mute¹³⁷); *coma vigil* is an alternative term for akinetic mutism¹³⁸.

Elective mutism, e.g. talking only at home and not at school, is due to emotional problems.

Diurnal variation of mood: mood varies with consistent 24-hour cycle that is independent of environment, e.g. in endogenous depression the mood tends to be worst in the morning and to lift as the day progresses.

Waxy flexibility (*flexibilitas cerea*) is found in catatonic schizophrenia (stuporose type); there is resistance to passive limb movement resembling that found on bending the candles of yesteryear. In maintenance of imposed postures the limb left in any position will remain there despite gravity.¹³⁹

Fantasy can be normal, even pleasant, unless it interferes with normal functioning. Mental life in schizophrenia is dominated by fantasy. In *Magical thinking* the person's thinking violates the normative understanding of causality, e.g. the belief that simply thinking or doing something will have an extraordinary effect on the environment. This reaches bizarre proportions in schizophrenia, but is normal in children and among those who live in isolated cultures. *Magical undoing* is a psychoanalytically-derived term that attempts to describing the underlying reasons for obsessional behaviour, e.g. a child who avoids cracks in the pavement is trying to avoid some unseen danger, or an obsessional patient performs a ritual in order to avoid harming others.

An *overvalued idea* is, according to Wernicke in 1900, a solitary, abnormal belief that is neither delusional nor obsessional in nature, but which is preoccupying to the extent of dominating the sufferer's life, e.g. the emaciated anorexic thinks she is obese, or the attractive dysmorphicphobic thinks she is ugly; it is comprehensible in the light of experience, family or culture; it is often immune to rational argument; and it may denote eccentricity rather than illness. It is not always easy to distinguish overvalued ideas from delusions. (Casey & Kelly, 2007, p. 39; McKenna, 2007, p. 331; Mullen, 2008, p. 24)

The term *zeitgeist* refers to the general intellectual and cultural climate of taste characteristic of an era.

Delusions may be primary or secondary.¹⁴⁰ (Jaspers, 1913/1963) Jaspers listed four primary delusions: *autochthonous* delusion (sometimes used synonymously with primary delusion), delusional perception, delusional atmosphere, and delusional memory. An *autochthonous* ('sprung from the soil') delusion (or

¹³⁵ Semantic dementia is associated with involvement of the left temporal lobe; dysfunction of the right temporal lobe is associated with prosopagnosia.

¹³⁶ 2% of 111 schizophrenic patients in one series. (Andreasen, 1987)

¹³⁷ Some catatonic patients may lie very still and yet sing; but strictly this is not 'mutism'.

¹³⁸ **Akinetic mutism** has a number of causes, e.g. third ventricular tumours or infarction of the cingulate gyri. (Barris & Schuman, 1953) Unlike in catatonic stupor, akinetic mutes will swallow fluids and food placed in the mouth, withdraw from painful stimuli, have not got waxy flexibility, and show no response to parenteral lorazepam. If primates have the anterior cingulate cortex lesioned they will not cry out mother leaves them.

¹³⁹ *Mitmachen* refers to an extreme form of obedience: the therapist is able to place patient's body part in any position without being resisted, the part slowly returning to its resting position. In *gegenhalten* the patient opposes passive movement with the same force used by the examiner. In *mitgehen* the patient moves in the direction of even slight pressure despite being asked to resist, as when an anglepoise lamp lifts with the simplest touch.

¹⁴⁰ Although *delusional explanation* is nowadays often used to describe certain secondary cases, e.g. 'I hear a voice coming from my mastoid bone. This means that there is a transmitter there'.

delusional intuition) arises out of the blue, is fully formed, and is unrelated to prevailing mood or recent events, e.g. 'I was walking down the ramp when I saw that the captain had a red rose in his buttonhole and then I knew that I was here to save the world.' A secondary delusion may arise from a primary delusion, e.g. 'I have the right to all famine-relief funds because I must raise an army of robots to defend the atmosphere against invading Martians.' Alternatively, a delusion may be secondary to a mood disorder, as when the depressive believes that 'I am so bad that I must have been put here to destroy everyone's happiness.' There is evidence from a small study (Colbert et al., 2010) that inflexibility of beliefs and extreme responding may characterise the thinking styles of people with delusions and that such characteristics may not be specific to the delusions themselves.

Delusions

May be *systematised* and/or *encapsulated*

Systemised - Delusion and its ramifications fit into complex, all-encompassing scheme that makes logical sense to the patient, e.g. being persecuted by an organisation, i.e. an elaborated delusion: a basic delusion is added to by other delusions derived from that basic delusion; more common in delusional disorder than in schizophrenia

Encapsulated - Apart from the delusion or its ramifications, the patient generally behaves in a normal manner, or at least is not perceived as especially unusual.

Mood-congruent delusions are in keeping with the prevailing mood, e.g. believing one is the Messiah when manic or damned when depressed; delusions which are *incongruent* with mood might be seen, e.g. in the manic who believes he is the victim of a Martian conspiracy or that his thoughts are being extracted by the FBI; this concept of delusions incongruent with mood has been criticised as leading to overlap with schizoaffective¹⁴¹ disorder. (Kendler, 1991) Hallucinations may (or may not) also be congruous with mood (depressive hears condemnatory voices). In fact, congruity and incongruity of clinical features in psychotic depression may be equally common in clinical practice. (Schweitzer & Parker, 2007, p. 183)

Monosymptomatic delusional states, where only a delusion¹⁴² separates the individual from his normal fellows, may respond to pimozide (Orap) or other antipsychotic drugs; *monosymptomatic hypochondriacal psychosis* has the same meaning as delusional disorder, somatic (sub-) type. (Munro, 1997) Primary delusions¹⁴³ are difficult to identify in clinical practice and might occur in conditions other than schizophrenia, such as epilepsy. The term *paranoid*¹⁴⁴ means 'resembling paranoia'¹⁴⁵, or simply 'deluded' or excessive self-reference but is often used, not very accurately, as a synonym for persecution. Munro (undated) has reviewed the phenomenology, nosology and treatment of 'paranoia'.

Delusions of persecution involve the false belief that people are out to do one harm - they are often quite bizarre in content. Analytically speaking, a delusion of persecution occurs when someone denies hostile feelings in themselves and attributes them to others; he is using denial and projection.

Partition delusion

Belief that a person, animal, object or radiation can pass through normally impenetrable barriers such as walls

Patient, classically suffering from schizophrenia, is usually convinced that the source is the house of a neighbour

¹⁴¹ Described by Jacob Kasanin in 1933.

¹⁴² Such as delusional *parasitosis*, or a delusion of *bromosis* (Gk. to stink – bromine being associated with a foul odour), i.e. that one emitting an offensive odour.

¹⁴³ Some authors dispute their very existence. (Freeman, 1981; Roberts, 1992)

¹⁴⁴ Gk. *para nous*: 'mind beside itself'. Paraphrenia, a relatively redundant term, (Hart, 1990) refers to a state of late onset, paranoid delusions, hallucinations, well preserved personality, and often auditory, or less commonly, visual defects. (Holden, 1987) The familial independence of paranoid psychosis from schizophrenia finds support from a study by Kendler, et al., (1985) who examined the family histories of patients with paranoid psychosis, schizophrenia, and medical illness. It has been argued by others that paranoid psychosis is a variant of schizophrenia (e.g. Schneider, 1959), an affective illness (Specht, 1901), or a separate nosological entity, distinct from both schizophrenia and affective illness (e.g. DSM-III-R, predecessor of DSM-IV).

¹⁴⁵ *Paranoia* = Gk, 'by the mind's side'.

Delusions of worthlessness occur in depressive psychosis. Nihilistic delusions ('my brain is rotten', 'my gut is clogged with cement', 'my liver is riddled with worms') are typical of Cotard's syndrome, (O'Shea, 2006) which may be due to depression, schizophrenia, or an organic brain syndrome. Delusions of grandeur ('I am God', 'I am a billionaire') may be found in organic brain conditions,¹⁴⁶ mania, or schizophrenia.

The belief that some unrelated event or object has special meaning for the individual is called a *delusion of reference*, e.g. the belief that the main evening news bulletin was put on for the patient's sole benefit. With *ideas of reference* (or *ideas of self-reference*) insight is retained but the feeling of being noticed cannot be ignored; the subject knows that he is the origin of the feelings that others are taking undue notice of him or discussing him; anxiety may spawn ideas of reference. *Delusions of control* (or *passivity*) are present if a patient believes that external forces (radio waves, telepathy, etc) can control his thoughts, words, movements or feelings.

There are many different diagnostic criteria for schizophrenia, e.g. Bleuler's 'Four As' (Affect, Associations, Ambivalence, Autism), Feighner's, RDC (research diagnostic criteria; Spitzer, ea, 1975), and Schneider's (1959).

Schneider's first rank symptoms (FRS)¹⁴⁷ are sufficiently often quoted to necessitate reproduction here:

Auditory Hallucinations: voices repeating ones thoughts aloud; voices anticipating ones thoughts; multiple voices discussing one or arguing about one in the third person; and voices commenting on ones thoughts or actions. The phenomenon of hearing ones thoughts spoken aloud may be classified as follows: if heard at the time of thinking them the term used is *Gedankenlautwerden*, and if they are heard just after thinking them they are called *écho de la pensée*. However, the patient may also hear his thoughts spoken aloud just before he thinks them. Sims (2003, p. 165) considers audible thoughts¹⁴⁸ to be an example of auditory hallucination. *Disorders of the possession of thought* include thought insertion, withdrawal and broadcasting. In *thought insertion and withdrawal* some foreign agency puts their thoughts into ones mind or removes ones own thoughts.¹⁴⁹ In *thought broadcasting* (*thought diffusion*) people can hear one think because ones thoughts are broadcast. This is different from the *delusion of mind reading* wherein the patient believes others can read their mind/thoughts, i.e. a subjective experience of others knowing ones thoughts without the belief that they can be heard aloud. Much of these distinctions may be purely semantic. Telepathy refers to the deliberate beaming of thoughts from one person to another.

Delusions of control: 'made' act, feelings, impulses refer to the belief that outside forces can make one feel or do things against ones will. If the temporal lobe is stimulated during surgery, patients may experience similar 'made' thoughts and feelings as are found in both the temporal lobe epileptic aura and in the psychoses. (Penfield & Rasmussen, 1950) According to Frith, (2004, p. 150) a delusion that someone else is moving ones arm is related to lack of attenuation of activity in the parietal cortex.

Delusions of Passivity: one is forced by outsiders to experience bodily sensations. *Delusional perception* is present when a delusional interpretation of a real perception is made; the perception is mundane and logically unconnected, e.g. 'I knew I was God when I saw the cat drink its milk', or a coat hanging in a shop window suggests that one is destined to be the next Pope. The term *delusional mood* (or *atmosphere*; *Wahnstimmung*) refers to the state of *perplexity* (usually unpleasant emotional state akin to bewilderment), foreboding, dread or anxiety occurring early during a psychotic breakdown, consisting of a variety of paranoid delusions which are transient and changing; the patient tries to make sense out of what seem to be unusual changes going on about him; he may recover or develop a stable delusional system¹⁵⁰. During the early formative or recovery stages of a delusion we can speak of a *partial* delusion, when the belief is held with less intensity. *Delusional memory* (retrospective delusion) refers to a delusional interpretation of an apparently real memory or a false memory¹⁵¹ arising in the context of psychosis, e.g. a deluded woman who

¹⁴⁶ E.g. GPI.

¹⁴⁷ Described by Kurt Schneider (1887-1967) in 1959.

¹⁴⁸ The hallucination of hearing ones own thoughts out loud may precede, coincide with, or follow the real thoughts.

¹⁴⁹ Thought withdrawal and thought blocking usually co-exist.

¹⁵⁰ This may be the same as the 'Truman syndrome' of Fusar-Poli ea (2008) who write about impending psychosis being associated with the feeling that the world has changed in some way that others are aware of, that one is the subject of a movie and living on a film set; the ordinary is different; there is a search for meaning; depersonalisation/derealisation; disturbed sense of ownership; fluid sense of self; distorted stream of consciousness; and a sense of disembodiment.

¹⁵¹ *Memory distrust syndrome* is due to *source amnesia* (cannot be sure where the information came from, self or others, so distrusts own memory).

believes someone is trying to kidnap her child recalls a man stopping her for directions some months ago and now 'realises' that he was really getting information that would aid him in the kidnapping. The content of delusions tend to keep up with the times, e.g. satellite TV dishes in the early 1990s (Kidd ea, 1992) and the so-called Truman syndrome (called after *The Truman Show* of 1998 starring Jim Carrey – a patient believes that he is trapped inside a reality show, that every movement is being filmed and that everything is contrived by TV producers).

Feighner's definition of schizophrenia (summary)

Chronic illness with at least 6 months of symptoms prior to index evaluation, without return to premorbid level of psychosocial adjustment

Absence of period of depressive or manic symptoms sufficient to qualify for affective disorder or probable affective disorder

Also, at least one of the following:

- delusions or hallucinations without significant perplexity or disorientation associated with them
- verbal production that makes communication difficult because of a lack of logical or understandable organisation (in the presence of muteness diagnosis must be deferred)
- at least three of the following social factors: single, a relative with schizophrenia, poor premorbid social adjustment or work record, absence of alcoholism or drug abuse within one year of onset of the psychosis, and onset of illness prior to age 40

Somatisation of affect occurs in depressives who complain of somatic symptoms instead of mood disturbance. The term *somatisation* was introduced by Stekel early in the twentieth century; Lipowski (1988) defined it as a tendency to experience and communicate somatic distress in response to psychosocial stress and to seek medical help for it; Murphy (1989) described it as the commonest way in which psychiatric disorder is presented to the GP - bodily symptoms are misattributed by patients to organic disease. Somatisers may be hostile to the idea of emotional dysfunction. (Murphy, 1989) In some cultures the healer shares the patient's explanatory model of somatic causation and diagnoses a physical disorder instead of an emotional one. The rise in popularity of 'somatoform disorders' in the US may reflect direct access to specialists and the easy accumulation of number of symptoms required for the diagnosis. Porter and Gorman (1989) point the finger at doctors' training, which stress the need to search for physical illnesses. Somatization can be a primary personality trait, or secondary and transient when under stress or depressed. *Alexithymia*, or alternatively *somatothymic*, (Yates ea, 1998) refers to a constricted ability to recognise and express feelings or emotional states. (Sifneos, 1973) Somatizers are said to have few dreams and to think in non-symbolical ways; they cannot discriminate between emotional states and bodily symptoms. Alexithymia may be mimicked by certain cultural expression styles and may be a state-dependent phenomenon, e.g. in depression. (Marchesi ea, 2008)

*Astasia abasia*¹⁵² is a hysterical symptom¹⁵³ involving a refusal to stand up or walk for fear of falling. The gait is bizarre and the patient cannot stand without assistance. The patient sways and almost falls.

Hysterical pseudodementia is very rare. Global amnesia has a sudden onset. The patient cannot recall anything. It probably always has a hysterical basis.

A dominant individual within a tight social grouping usually starts *epidemic hysteria*. Hyperventilation may be an important element. A background of tension and apprehension is often found in the group. Treatment involves quick recognition, isolation of affected individuals, psychological explanation and reassurance, use of local traditional healing methods (Skuse, 2007), and the delivery of mental health education programmes to the community. (see Puella, 1986).

Insight: Poor insight in psychiatric patients is associated with non-compliance, social dysfunction, and delayed presentation. Insight into psychiatric disorder is not a uniform phenomenon; and it must be rated on a continuous rather than a dichotomous scale. Rather than saying that insight is present or absent, we should ask if the patient knows that he is acting abnormally, thinking abnormally, or experiencing abnormal

¹⁵² Also called Blocq's syndrome after Paul-Oscar Blocq (1860-96).

¹⁵³ Conversion disorder (DSM-IV) or dissociative motor disorder (ICD-10).

perceptions; if he thinks that the foregoing problems are due to mental disorder or does he blame something else, e.g. somatic disease or poisoning by others; and if he thinks that treatment is necessary?¹⁵⁴

Sophisticated testing suggests that very few acute voluntarily admitted patients can understand the need for neuroleptic drugs. Unawareness of illness in schizophrenia, on MRI evidence, might be related to small intracranial volumes, i.e. brain and CSF combined. Reduced general neuropsychological functioning and grey matter deficits in the posterior cingulate gyrus and right precuneus/cuneus may be important in lack of insight in first-onset psychosis.(Morgan ea, 2010) Factors that influence insight in psychosis are cultural beliefs, IQ, knowledge, the physician-patient relationship, symptomatology (e.g. lack of insight into delusional beliefs, or preserved insight associated with depressed mood), executive function¹⁵⁵ (initiation, selection, and monitoring of activity, and contextual coding) deficits, denial¹⁵⁶ (motivation, preservation of self esteem, stigma avoidance), and personality traits. High IQ scores were associated with better insight in psychosis of recent onset. Descriptions of ‘insight’ should be detailed. The *Insight Scale* (Marková & Berrios, 1992b) is 32-item instrument, can be observer- or patient –rated and purports to measure insight and changes therein.

There are many examples of cases where the patient is hallucinated but *retains insight*. Partial seizures can be associated with visual, auditory, olfactory, or gustatory hallucinations with retention of insight. Tactile hallucinations secondary to cocaine or amphetamines are another example. The same applies to olfactory hallucinations due to migraine or, rarely, damage to the olfactory bulb/nerve. Similarly, auditory hallucinations due to pentoxifylline, deafness (with musical hallucinations – see Miller & Crosby, 1979), and lesions of temporal lobe or pons, can be accompanied by retention of insight. Visual hallucinations can occur during bereavement (visions of a lost one), because of sleep loss, or when falling asleep. Visual hallucinations with insight may also be found with migraine, narcolepsy (hypnagogic), Charles Bonnet syndrome,(Q.V.) lesions of the cortex (including in an hemianopic field), lesions of the cerebral peduncles (*peduncular hallucinations*) or pontine tegmentum (*‘Pick’s visions’* wherein people are seen walking through distorted walls), cocaine, amphetamine, solvents, PCP, other hallucinogens (including flashbacks), quinidine, trazodone, maprotiline, propranolol, L-DOPA, digoxin, and TCAs.

For the patient in psychotherapy, self-observation is insufficient for true insight. What is needed if real change is to occur is emotional¹⁵⁷, as distinct from intellectual, insight.(Donnelly ea, 1970) *Isolation of affect*¹⁵⁸ may be associated with pseudo-insight as when a patient gives an intellectualised account of his dilemma without any associated feeling.

Quality of life

Quality of life is a difficult concept to define and attempts at measuring it have varied from generic (independent of specific disease) to disease-specific instruments.(Katschnig & Krautgartner, 2002) Doctors and patients evaluate this from different perspectives, e.g. bipolar patients in remission have reduced quality of life (Goosens ea, 2008) and the doctor may be happy with the control of delusions whilst the patient may be unhappy with living in a tenement.(Naber, 2003) However, patients with chronic mental disorders may equally set their aspirations at a lower level than might a person not so affected.

One can measure health intervention outcomes in terms of quality (score 1 for perfect health, 0 for no quality, minus scores for ‘better off dead’) and quantity (life expectancy) of life. Quality and quantity are

¹⁵⁴ The majority of patients with schizophrenia in one study (Amador ea, 1994) were unaware of important aspects of their illness and almost one quarter were almost completely unaware of the efficacy of treatment. Those with affective disorders had less severe lack of awareness, although manics more closely resembled schizophrenics in this regard. Schizophrenic patients in remission were just as unaware as were those who remained psychotic. Hence, lack of awareness seemed to be trait that is resistant to treatment. It might relate to prefrontal cortical dysfunction. On the other hand, David ea (1992) found that compliance only weakly related to ability to label psychotic phenomena as abnormal. Murray (2003) points out that delusional beliefs developed during a period of psychosis may persist despite clinical improvement, e.g. ‘the KGB are no longer trying to harm me, but they were doing so!’ Pini ea (2001) found that schizophrenia and bipolar affective disorder were associated with less insight than was the case with schizoaffective disorder and psychotic unipolar depression. David ea (1992) could find little relationship between insight and age, sex, diagnosis or number of hospital admissions.

¹⁵⁵ Neuropsychological dysfunctions, specifically impaired set-shifting and error monitoring, were found to interfere with insight in psychosis in a meta-analysis.(Aleman ea, 2006)

¹⁵⁶ Adaptive or maladaptive depending on engagement with services/treatment.(Cooke ea, 2007)

¹⁵⁷ Capacity to feel and respond to understanding.

¹⁵⁸ A thought or memory is subconsciously divorced from associated emotion.

combined as quality-adjusted life years (QALYs).¹⁵⁹ If, for example, a treatment gives one 5 additional years of life with an average quality of life rated as 0.6 the yield would be $5 \times 0.6 = 3.0$ QALYs.

Classification¹⁶⁰

'Then, we will gradually arrive at the stage where we will be able to separate out individual diseases from the larger categories of our textbooks and sharpen their clinical definition.' (Alzheimer, 1907)

'A classification is a way of seeing the world. It is the reification of an ideological position, of an accepted stand of theory and knowledge ...A classification can remain alive and be improved only if it is constantly re-examined in the light of new knowledge.' (Sartorius, 1989)

'... if a single diagnostic system is allowed to dominate our thinking we limit our nosological options and narrow the chances of finding the cause(s) of the disorder.' (Farmer & McGuffin, 1989)

'... the disorders were created by fiat rather than empirical research.' (McKeon, 1993)

'...theory has its place, but it does not stop things from existing.' (Finger, 2000)

'Multiple diagnoses with simultaneous treatment for each of the diagnoses – as if they are equally important – has been replacing prioritizing diagnoses and treating a primary disorder.' (Scheiber, 2003)

'We do not yet and probably never will possess a diagnostic construct as simply and clearly measured as temperature.' (Kendler, 2009)

Four major types of classification (Jablensky, 1988)

Empirical - based on observed fact, e.g. histology

Inferential - possesses shared hypotheses, e.g. division of depression into reactive v endogenous

Monothetic - units placed in classes according to variations along one dimension, such as IQ

Polythetic - arrange units into classes that share many properties, e.g. the psychoses

The ideal classification is both comprehensive, encompassing the whole range of phenomena, and mutually exclusive (containing no overlap), an almost impossible wish in a soft discipline. (Schatzberg et al., 2005, p. 14) The legal profession is often guilty of referring to 'clinical guidelines and diagnostic manuals' as if they were an exact science. (Simon, 2003, p. 1619) Fonagy and Paris (2008, p. 103) suggest that guidelines (for psychotherapy) cannot replace clinical skill.

Psychiatric nosology is subject to constant review. There are many reasons for this, such as changing patterns¹⁶¹ of mental illness, geographical differences in diagnostic practice, (Cooper, et al., 1972; WHO, 1973; Kendell, et al., 1974), and the sheer diversity of combinations and permutations of symptoms which are possible in psychological medicine. The symptoms exhibited by a drug dependent person, for example, depend on the type, quality and dose of the drug used and the presence of contaminants; and the previous experience and expectations of both the user and others sharing the experience. Simply deciding if someone is deluded or not may be rendering the world more simple than it actually is. (Kaplan et al., 1994)

Entitlement to care, particularly in the USA, has become to depend on so-called diagnosis-related grouping (DRG). Diagnosis is now much more open to scrutiny than in the past. No longer is it simply a convenient shorthand between clinicians'. (Mace, 1992)

While most psychiatrists see the need for some sort of taxonomy, such a position is not universal.

Taxonomy is useful if it suggests possible causes, says something about likely outcome, and points the way towards rational management. It should serve as a powerful communication role. Rigidly adhered to *operational criteria* (category specified by series of precise inclusion and exclusion statements) carry good reliability (precision) but questionable validity (excessively broad scope). (Farmer & McGuffin, 1989; Farmer et al., 1991; Millon & Davis, 1996) *Operational definitions* are in increasing use. They started in St Louis in 1972 and were adopted by DSM-III in 1980. Rules are laid down for reaching a diagnosis, e.g. how many symptoms from a list have to be present and what must be absent, how long must be the history, and so on; before this approach there existed only thumb-nail sketches of disorders.

Classification may help, via the statistical returns from treatment agencies, in the planning of mental health services and legislation.

¹⁵⁹ Some ethicists believe that the QALY discriminates against old people when it comes to resource allocation (e.g. drugs for Alzheimer's disease) because they have fewer years of life to preserve. (Hoey, 2007)

¹⁶⁰ Classifications are simply 'fictions imposed on a complex world to understand and manage it'. (Marks & Mataix-Cols, 2004)

¹⁶¹ Hare (1998) suggests the nature of mental illness is mutable in the same way as diseases like scarlet fever changed in terms of virulence; he points out (p. 38) that evolution of living creatures were assumed to be immutable during the 18th century and that pre-Darwin physicians and naturalists respectively did not consider that diseases and plants could arise *de novo*.

Sources of variance in diagnosis

The diagnostician

- (a) Different information elicited from patient/other sources
- (b) Using different thresholds of diagnostic significance for what is elicited¹⁶²
- (c) Reliance on different theories of causation, e.g. biology v social (criterion variance)

The patient/subject/client

- (a) Real inter-patient differences
- (b) Similarities/overlap of symptoms/signs between different disorders
- (c) Changes in manifestations over time

Levels of reliability according to diagnostic grouping

High – organic disorders such as amnesic syndrome

Mid-level – functional psychotic disorders, e.g. schizophrenia

Low – neuroses (e.g. generalised anxiety) and disorders of personality

Some disadvantages of current classification

Tells us little about cause, symptoms, treatment, or prognosis

Squeezes people into niches whereas most cases are interforms (low reliability; intersyndromes, not otherwise specified, rag-bag, dustbin or catch-all categories – American insurance may be reluctant to pay for anyone without a ‘hard’ diagnosis!) (Barraclough & Gill, 1996); not elsewhere specified ends up with the majority of cases (Farmer ea, 1992; Widiger & Mullins-Sweatt, 2007, p. 7)

It is pejorative (e.g. ‘schizophrenic’, ‘hysterical’, ‘antisocial’)

Labels give us a false sense of understanding and encourage naïve assumptions about disease entities

Childhood disorders (e.g. separation anxiety) may present to the adult psychiatrist and adult disorders (e.g. depression) to the child psychiatrist (Shear ea, 2006)

There is no quantitative divide in Nature between ADHD and normal children in terms of ability to attend, between dieting and eating disorder in adolescents, and between just enough and too much alcohol intake (e.g. Rey ea, 2007, p. 390)

Spitzer’s (1983) ‘LEAD’ approach to diagnosis is too cumbersome for clinical use: Longitudinal (v cross-sectional), Expert (opinion), All Data (e.g. old case-notes).

Grouping problems

categories e.g. schizophrenia, affective disorders, etc. - good for discrete entities and individual patients

dimensions e.g. euthymic to very depressed¹⁶³ - useful for research¹⁶⁴ (gives more statistical power)

multiaxial form - DSM is the classical example

All current diagnoses are simply working hypotheses and ‘should not be regarded as sacrosanct’. (Tyrer, 1996) Dimensions and categories are not necessarily mutually exclusive and one or both may best suit an individual problem. Attempts are being made to create combined dimensional and categorical diagnoses. (Helzer ea, 2006; Cole ea, 2008; Demjaha ea, 2009)

The influence of culture, a concept that is defined in many diverse ways, (Gaw, 2001, p. 2) is discussed in the box.

¹⁶² However, where does one place the threshold for depression? There is evidence that ‘subthreshold’ depression is (a) on a continuum with ‘clinically significant’ depression, (b) that it interferes with health, (c) that it shares risk factors with more severe cases, and (d) that it occurs worldwide. (Ayuso-Mateos ea, 2010)

¹⁶³ 4 weeks fluoxetine led to more positive affect and increased social facilitation in normal people. (Knutson ea, 1998)

¹⁶⁴ Prisciandaro and Roberts (2009) found that dimensional models had greater predictive validity than did a categorical (DSM major depression) model of unipolar depression.

Culture and psychiatric presentation

Indigenous communities suffered greatly from exploitation, expulsion, slavery, disease, genocide, sexual abuse, loss of tradition and legal redress during the era of colonisation. In some cases their children were forcibly removed and reared by white settlers. In many cases the effects can still be seen today, e.g. in high rates of poverty, indebtedness, illiteracy, unemployment, alcohol-related problems, depression and suicide. It is debatable whether true ('entities') 'culture-bound' syndromes exist or whether these are simply universal phenomena modified by local culture.¹⁶⁵ Bhugra et al (2007) suggest that they be viewed as symptom complexes, modified by culture, occurring in response to stressful circumstances. Race, culture and ethnicity may falsely appear to explain research findings when factors such as economics (poverty, debt, education, etc) are not examined. (Patel & Kleinman, 2003) Studies that look at a sample from a tiny part of a huge country (e.g. China) may wrongly claim to be representative of the country as a whole. One of the points against someone having a delusion is that they share their belief with their culture. Nevertheless, psychopathology causes considerable personal and socio-economic disability across cultures. A discussion of cultural influences on schizophrenia is to be found in the chapter on schizophrenia. Religion influences psychopathological content (Koenig, 2009), e.g. the more orthodox a Jew the more likely is the content of obsessions to have a religious theme. (De Silva & Rachman, 2004, p. 62) Cultures that promote *individualism* (egocentric) may lead to a different mode of expressing distress to those that value *collectivism* (sociocentric), e.g. loneliness and guilt versus shame and unfulfilling interpersonal relationships respectively. Although not universally corroborated, ethnic minorities may tend to express distress through somatic complaints. There are a number of possible reasons for this, e.g. stigma surrounding mental illness, language, and non-recognition of Cartesian dualism, i.e. the mind and body are not distinct from one another.

According to Bhugra (2008) a culture may be:

Pathogenic – causing symptoms

Pathoselective – effecting groups in different ways

Pathoplastic – modifying symptom presentation

Pathoelaborating – reinforced by culture

Pathofacilitative – some cultures are prone to certain disorders

Pathodiscriminating – culture defines what is deviant

Some key terms require definition. *Acculturation* is the assumption of characteristics of the larger or more advanced society. *Assimilation* (a bigger step than acculturation) involves total absorption in the larger society. Examples of maladaptation to a host culture include 'over-identification' (decry old culture in favour of host practices) and 'hyper-identification' (decry host culture in favour of culture of origin). A more comfortable adaptation is represented by 'inside-outside split' (private practice of culture of origin and public practice of host culture). *Etic*¹⁶⁶ refers to a socially unique, intra-cultural perspective, e.g. *susto* or the *fallen fontanel syndrome* of Mexico. *Ethnography*¹⁶⁷ consists of the examination of written records, folk tales, myths, language, key informants, life histories, questionnaire surveys, psychological tests, and participant observation, all aimed at studying cultural forms. The Hmong of Southeast Asia believe that the soul is always in danger from opportunistic spirit thieves called *dabs* and that shamans¹⁶⁸ (*tvix neeb*) who are skilled in spirit rescue oppose such forces; medical interventions break sacred Hmong taboos and the Hmong will only seek medical help as a last resort and with little tolerance for lack of results. (Fadiman, 1997) *Etic*¹⁶⁹ denotes universal, cross-national concepts, e.g. poliomyelitis or Grave's syndrome. An example of a *multiethnic country* would be the USA. However, the values of the white middle class are predominant¹⁷⁰. *Psycholinguistics* is the study of language and its communicative function. The latter must be taken into account for cross-cultural studies to be valid.

¹⁶⁵ E.g. absence of fat phobia in some Chinese anorexia nervosa patients. (Lee et al, 1993)

¹⁶⁶ From 'phonemic'.

¹⁶⁷ Gk *ethnos*, race.

¹⁶⁸ Shamans use verbal and ritual healing methods (as do medicine men) and, in an altered state of consciousness, communicate with ancestors/spirits, and recover the ill person's soul. Diviners read oracles, interpret dreams, and communicate with the spirit world (incl. the dead). Herbalists use plant remedies, active or sham.

¹⁶⁹ From 'phonetic'.

¹⁷⁰ WASP, White Anglo-Saxon Protestant. African Americans with bipolar or psychotic mood disorders are at increased risk of being misdiagnosed as having schizophrenia, i.e. mood symptoms may be discounted and psychotic symptoms given priority by clinicians;

Attempts have been made to match the following syndromes to Western disorders, although this practice has been criticised. (Kay & Tasman, 2006, p. 253) It is more important to grasp the broader issues surrounding culture than to focus on these syndromes. Also, the unthinking global application of Western taxonomies may be mistaken. (Summerfield, 2008) A person could simply be reacting normally to dreadful local circumstances.

Americas

Ataque de nervios (Puerto Rican syndrome) is found among Latin American Hispanics, especially older females with relatively little education. It is a socially sanctioned expression of grief or conflict consisting of anxiety and aggressiveness leading on to paresis, loss of consciousness or blanking out of the mind, hyperventilation, shouting and swearing, striking out at others, falling, convulsive movements or lying as if dead, and amnesia. It may be brief and mild, severe and prolonged, and it may be recurrent. Dissociative and somatoform mechanisms have been proposed for this phenomenon.

Billis (muina, colera) is considered to be due to disturbed relationships between bodily hot and cold and between spirit and soma as a result of anger or rage in Latinos. Acute tenseness, screams, shakes, headache, and upset stomach are common, whereas some cases appear to lose consciousness. Sufferers may be left bereft of energy for long periods.

Bouffée délirante is found in Haiti and West Africa and may resemble brief psychotic disorder. Sudden onset of agitation, aggression, excitement, and confusion characterise his phenomenon, with some cases experiencing hallucinations and paranoid thinking.

Evil eye (mal de ojo), mainly found in Latin America (particularly children), refers to illness induced by the stare of a jealous person. Broken sleep, crying, gastrointestinal upset, and fever may occur. By way of comparison, ancient Ireland had its *Cailleach*, an old hag who was able to transfer mental illness from one person to another. In early Ireland the *madman's wisp* was made from a ball of straw or grass by a Druid and then thrown in someone's face. The unfortunate victim went mad.

Falling out (blacking out, indisposition) is a dissociative state found among excited or fearful black Americans, Bahamians and Haitians in Miami, consists of sudden collapse, paralysis, and an inability to see or speak. Hearing and understanding are, however, intact, and no evidence is uncovered to suggest an epileptic origin.

Ghost sickness among American Indians involves preoccupation with death and the dead. There may be an element of witchcraft. Sufferers may report nightmares, weakness, dread/anxiety/suffocation/futility, confusion, loss of consciousness/faintness/dizziness, anorexia, and hallucinations.

Grisi siknis is seen among the Miskito of Nicaragua. The symptoms include headache, anxiety, irrational anger directed towards nearby people, and aimless running and falling.

Hi-Wa itek in Mohave Indians may follow unwelcome separation from a loved person. Anorexia, depression, suicide, and poor sleep are among its manifestations.

Kayak angst, or anxiety about drowning at sea, is found among the Inuit.

*Locura*¹⁷¹ of Latin America is a chronic, severe psychosis attributed to heredity or life's problems in which there are agitation, visual and auditory hallucinations, incoherent speech, inability to adhere to societal rules, and with the potential for violence.

Piblokto or *pibloktoq (running syndrome)* occurs in 'hysterical' Eskimo females who may run away or jump into cold water; she is at risk of killing either herself or others, and she has no memory for the event once it is over; it is viewed as representing a dissociative fugue.

Susto (chibih, espanto, pasmo, perdida del alma, tripa ida) occurs in the High Andes and takes the form of a sustained melancholia due to worries that the soul may vacate the body.

Tabanka is found in Trinidad among males who become depressed and suicidal once deserted by their wives.

Windigo is found among the Cree Indians of Canada. A Windigo is a mythical monster. Some tribesmen, during periods of economic hardship, believe that they have become this ghoul, and they have been known to murder and eat their brethren. Trivial symptoms (e.g. nausea or hunger) may lead to great upset lest they suggest imminent transformation.

Africa¹⁷²

Amariko, an Ugandan colouration of post-partum psychosis, involves a wish on the mother's part to eat her baby! Local beliefs about promiscuity and legitimacy may play some role in aetiology.

Brain fag syndrome (Ori ode or Ode ori) in Nigeria is a prevalent form of somatised anxiety and depression found in association with education in West Africa. It is characterised by a rich variety of somatic symptoms, particularly related to the head (e.g. parasites felt crawling about inside the head when experiencing upset), excess autonomic activity, cognitive symptoms such as poor concentration and retention of new information, and visual symptoms. It has been suggested that the condition may be a response to excessive expectations in, and cost of, education. Another interpretation is that it is panic disorder modified by culture.

Obeah is found among Africans and Asians. The health and wellbeing of a person can be influenced by the actions of a distant other person. It is easily misdiagnosed as a paranoid disorder. Treatment is through the ministrations of a traditional healer (or priest if the victim is Christian) who lifts the curse.

Possession states, e.g. that a ghost occupies one's body, should not automatically lead to a diagnosis of mental disorder. Instead one should discover the personal and communal meaning of the experience; the relatives should be interviewed, using an interpreter as necessary. *Sangue dormido*¹⁷³ among the Portuguese-speaking Cape Verde islanders (or emigrants from these Atlantic islands) consists of numbness, pain, tremor, stroke, blindness, infection, heart attack, and, in pregnant women, miscarriage. *Sar* (or *zar*) is a

African Americans receive higher doses of antipsychotics, are more likely to be on a depot neuroleptic, to be involuntarily hospitalised and to be placed in seclusion, and to be over-sedated (in case of violence – even in the absence of such a history) than are Whites.

¹⁷¹ Derived from adjective *loco* meaning 'crazy'.

¹⁷² Lifetime prevalences were higher in rural than in urban centres for psychoses in adults (4.4% v 1.6%), mental retardation (1.9% v 1.3%), and seizure disorders (4.0% v 1.6%) in a random selection of households in Mozambique. (Patel et al., 2007) Key informants most often attributed psychoses to supernatural origins, followed by seizures. The local traditional healer was the person most often consulted.

¹⁷³ *Sangue* = blood; *dormido* = sleeping (Spanish).

possession state in Somali women; Sar spirits hate men; and outrageous female behaviour may be legitimised by claiming to be possessed! Possession states are universal and are not unknown to Irish psychiatrists. *Ufufunyane*¹⁷⁴ is found among Zulu- and Xhosa-speaking people of southern Africa and is attributed to malicious witchcraft, spirit possession, or poison. Features include pseudolalia¹⁷⁵, paralysis, seizures, nightmares with sexual content, trance, and loss of consciousness.

Asia

*Amok*¹⁷⁶ ('to run amok'), found in Malaysian men (similar to *cafard* or *cathard* in other parts of SE Asia, *iich'aa* among the Navajo, and *mal de pelea* in Puerto Rico and Papua New Guinea), may be a manifestation of hysteria or part of another mental illness. Affected people are usually young or middle-aged living away from home and who have a recent experience of loss (including loss of face) or of being insulted. The victim becomes withdrawn, has outbursts of aggression, may kill or commit suicide, can develop exhaustion, and has amnesia for the episode once it is over.

Latah is found in Malaya with similar conditions being described elsewhere (*amurakh*, *ikota*, *imu*, *irkunii*, *myriachit*, *mali-mali*, *menkeiti*, *olan*, *jumping*, *silok*, etc). People startle easily. There may be echopraxia, echolalia, command obedience, and dissociative/trance-like behaviour. Others may take advantage of affected individuals and subject them to sudden frights in order to elicit startling. The typical victim of *latah* is a woman of low socioeconomic status.

Anthropophobia, described in Japan, mainly affects males who blush easily, show anxiety in face to face contact, and fear rejection. In Japan the self is subordinate to the community and fear of causing offence is socially sanctioned. Western diagnoses that must be considered include social phobia (Ballenger, 2004) and avoidant personality style or disorder. *Taijin kyofusho* (interpersonal fear) is probably the same syndrome (sufferers report that body parts/functions offend other people, e.g. odour, spoken thoughts, blushing, gaze/expression). Shame, which is a symptom of this syndrome, is very important in Japanese culture. It appears to respond to SSRIs. *Dhat* (*jiryān*; also *sukra prameha* in Sri Lanka) is a 'neurotic' disorder common in India. The term derives from the Sanskrit for bodily 'elixir'. The sufferer believes that a white 'discharge' in his urine consists of semen. The notion that semen possesses precious and life-preserving properties is deeply ingrained in Indian culture; therefore, its loss in any manner may be viewed as harmful. The *dhat* syndrome, originally described by Wigg, includes vague physical complaints, such as fatigue, anxiousness, anorexia, and guilt feelings. There may be sexual dysfunction, either impotence or premature ejaculation, which the patient attributes to loss of semen in urine due to excessive masturbation or sexual intercourse. The patient may describe a white discharge that is not confirmed on examination. An overvalued idea may form that the urine is foul smelling and less viscous than normal. *Shenkui* (or *shen-k'uei*) occurs in China and consists of anxiety, panic, and various physical complaints (including tiredness and sexual dysfunction). Again, excessive loss of semen by any means is believed to be causal. The author has certainly seen anxious Irish adolescents who imagined that they have semen in the urine due to 'damage' induced by masturbation, so the syndrome is more widespread than India.(Sumathipala ea, 2004) The importance of alleged falling sperm counts in Western males assumed almost hysterical proportions during the mid-1990s.

Frigophobia, found in East Asia, involves an excessive fear of the cold (wears far too many clothes). The person is concerned with loss of vitality. It may be related to OCD.

Hwa-byung (*wool-hwa-byung*; 'fiery illness' or 'illness of anger') is found in Korea, mainly in women. There are an epigastric mass sensation, anorexia, anxiety, dyspnoea, and epigastric pain. It seems to be reactive to social circumstances (a way to release anger or indignation), although partial improvement with antidepressant therapy has been recorded.

Bebainan is believed to result from sorcery among the Balinese.(Suryani, 1984) Sudden subjective confusion, tearfulness, screaming and shouting, especially in women and generally commencing between 16 and 30 years of age, occur in attacks usually lasting for 15-60 minutes. There is usually awareness of the attack whilst it is happening and it can be recalled later. It may represent a way of expressing feelings without incurring adverse consequences.

Koro (Malaysian for "head of turtle"; *rok-joo* in Thailand; *jinjinia bemar* in Assam; also called *suk-yeong* by Cantonese Chinese: shrinking penis) resembles panic in symptomatology. Sims (2003, p. 234) suggests that it's a form of *desomatization*, i.e. depersonalisation localised to one organ. *Koro* occurs in China and down as far as Indonesia. The victim, who usually has no history of psychopathology, believes that the secondary sexual organs (penis, female genitalia, breasts) are retracting (as does a turtle's head) into the trunk. He, or she, may take active steps to maintain the externality of breasts, penis, and so on. There is a tendency toward spontaneous remission. It is probably a non-specific symptom, especially in the West, having been described in both schizophrenia and bipolar affective disorder. It was described also in a patient with a corpus callosum tumour.(Durst & Rosca-Rebaudengo, 1988) This author has seen a few cases in Irish patients. Prognosis is much better in Asia than in the West.(Griffith ea, 2003) Interestingly, in Chinese folklore, ghosts have no genitalia!

Qi-gong reaction is a transient neurotic or psychotic response to practicing *qi-gong*¹⁷⁷ in China.

Shenjing shuairuo (Mandarin Chinese: 'weakness of the nervous syndrome') is known to us as neurasthenia.

Shinkeishitsu, found in Japan, consists of obsessions, perfectionism, ambivalence, social withdrawal, neurasthenia, and hypochondriasis.

Shin-byung is found in Korea where it is attributed to ancestral spirits: initial anxiety and somatic complaints give way to convulsive movements and anorexia. *Hsieh-ping* in Taiwan is somewhat similar: short-lived trance state whilst possessed by ancestral spirit who may be attempting to communicate with the family through the possessed; auditory or visual hallucinations, delirium, and tremulousness.

New Zealand

Whakama (shame) is expressed by Maori people when they break social taboos.(McKendrick & Ryan, 2007, p. 452) Despondency, agitation, anxiety, and unusual thinking may mimic mental disorder. *Whakamomori* consists of low mood, sometimes with damage to

¹⁷⁴ Person or voice that enters and controls a person (Zulu). The same condition is called *saka* in Kenya.

¹⁷⁵ Nonsense speech or babbling, as distinguished from glossolalia (speaking in tongues).

¹⁷⁶ The story of Ajax (in the Sophocles play written 5th century BC) and the sheep is sometimes given as an example of amok. However, the slaughter of the sheep by Ajax was an act of jealousy. Achilles' armour was given to Odysseus instead of to Ajax.

¹⁷⁷ This is a folk health-increasing practice which involves working with *qi* (energy) within the body. It may involve movement, breathing regulation, or focusing on 'energy centres' in or around the body. *Qi* or *qigong* = air, breath (Chinese).

self or others. *Mate Maori* (Maori sickness), which different forms, is due to the spirit world responding to the breaking of rules. Rules may be broken by the patient or by others (alive or deceased) in the *whanau* (extended family). This belief is reminiscent of western beliefs that TB or mental illness could be due to ancestral excesses (alcohol, masturbation, etc).

Early studies of mental disorders shared problems of observer bias, sampling errors, and non-standardised measuring instruments. Initial reports of a lack of depressive guilt in developing countries may not have been entirely accurate, as it has been demonstrated to exist, especially in Uganda. It has been suggested that Afro-Caribbean's are more likely to be detained as offender patients.

Psychologists Li ea (2007) discuss common difficulties in assessing, diagnosing, and treating minorities: flawed approaches to assessment (e.g. norms derived from mainstream culture); culture influences on experience and expression of symptoms (e.g. dissociation or depression); ignorance of norms, behaviours, and values; racial and cultural biases in the clinician; non-realisation that there may be greater differences between individuals from the same minority group than exists between the mainstream and the minority groups; lack of empirically based norms for administering/interpreting psychometric instruments; and inadequate training.

According to Ruiz (2007) the following ethnic considerations apply to prescribing psychotropic medication (relative to Caucasians):

- *Asians* – need less neuroleptics (haloperidol, clozapine), lithium or TCAs to get same results; side-effects are more severe
- *African/Blacks* – need smaller doses of TCAs and SSRIs, higher doses of clozapine and olanzapine, but equal doses of risperidone
- *Hispanics* – need lower doses of typical neuroleptics and some atypical antipsychotics (e.g. risperidone) for schizophrenia, and smaller doses of TCAs (they complain more about TCA side effects)

There are many published papers which report that people from developing nations are more likely to be diagnosed as having schizophrenia, to be admitted as involuntary patients, and to be less often offered psychotherapy.(cf. Bhugra & Bhui, 2001)

Services for ethnic minorities need to be accessible, provide trained interpreters¹⁷⁸, employ members of the minority group, and supply patient advocates. Realisation requires availability and considerable capital funding. Ireland and other countries are experiencing immigration in large numbers and provision remains inadequate.(Kelly, 2004; Skuse, 2008) Access to treatment by the elderly in ethnic minorities may be suboptimal, even in economically advanced countries.(e.g. Medicare in the USA: Virnig ea, 2004)

Provision of mental health services in the poorer nations of the world need to be adressed with more urgency than heretofore.(Jacob ea, 2007) Greater involvement of GPs and nurses may provide part of the answer to manpower shortages.(Ghebrehwet & Barrett, 2007)

Among the systems of classification used are: ICD - International Classification of Diseases, currently the tenth edition (ICD-10), from the World Health Organisation (WHO, 1992), the official one worldwide¹⁷⁹, and available in many languages and in clinical, research and GP formats; and DSM - The Diagnostic and Statistical Manual of the APA - currently the fourth edition (APA, 1994) with text revision (DSM-IV-TR).(APA, 2000) A national system available in English only¹⁸⁰, the DSM was introduced in 1952 as an alternative to an unpopular ICD-6 and has become less psychoanalytically orientated with progressive editions. Its early editions were much influenced by Karl Menninger and Adolf Meyer. ICD-10 includes psychosocial problems confronting the patient in axis III but does not include social consequences of a disorder among its guidelines and criteria, whereas DSM-IV includes significant impairment in social, occupational and other areas of functioning, concepts derived largely from Kraupl-Taylor.(Kraupl-Taylor, 1971) This clinical significance criterion may be virtually redundant in major depression (Wakefield ea, 2010), i.e. the intended role of the criterion in reducing false positive diagnoses may be small.

¹⁷⁸ Whilst awaiting an interpreter an emergency 'multilingual aid box' may be used. This contains a language identification card, a set of 20 translated phrasebooks and a user manual.

¹⁷⁹ Mental disorders were first specifically included in ICD-6.(Blacker & Tsuang, 1999) DSM-V (www.dsm5.org) and ICD-11 are due in 2013 and 2014 respectively.

¹⁸⁰ Although there is a 1995 'international version'.

Examples of computerised diagnostic programs are DIAGNO (Spitzer & Endicott, 1968) and CATEGO (Wing, ea, 1974). The French have clung tenaciously to their own idiosyncratic nosology. (Pichot, 1984) The label *functional* refers to 'those conditions which do not have a tangible organic causation'. (Mahendra, 1985) Crow (1986) has argued that there may be a continuum of psychosis¹⁸¹ extending from unipolar, through bipolar affective illness and schizo-affective psychosis, to typical schizophrenia, with increasing degrees of defect; genes predisposing to psychoses have a degree of stability, the form of psychosis tending to remain the same within families, but there is also the possibility of change.

As stressed by Cohen (2003, p. 6) 'disorder' is not synonymous with mental illness or disease.

ICD-10 (Chapter V, F)

Theoretical implications are avoided in ICD-10, which is generally an improved version of ICD-9. (Sartorius ea, 1993) Instead of following the neurotic-psychotic dichotomy of its predecessor, disorders are arranged in groups according to major common themes or descriptive likenesses, e.g. cyclothymia is grouped with mood disorders rather than disorders of adult personality and behaviour. The term neurosis is, however, retained. Homosexuality *per se* is omitted. As with DSM, provision is made for the employment of multiple axes.

ICD-10 axes (mirror axis in DSM-IV shown in brackets)

I – psychiatric disorders, mental retardation (intellectual disability), medical disorders (I, II, and III)

II – DAS-S, short disability assessment schedule to assess disability arising from axis I (GAF in V)

III – psychosocial difficulties confronting the patient (IV)

Social deviance or conflict on their own, without personal dysfunction, do not merit inclusion. The term *disorder* refers to 'a clinically recognisable set of symptoms or behaviour associated in most cases with distress and with interference with personal functions'. As many diagnoses may be recorded as are necessary to cover the clinical picture.

Goldberg's (2010) criticisms of DSM/ICD

High rates of comorbidity are products of diagnostic rules

Increasing use of 'not elsewhere classified' by practicing clinicians

Each edition gets bigger and more complicated

The term *hysteria* is dropped, because of its many meanings, and the term *dissociative* covers both dissociative and conversion phenomena. ICD-10 is sceptical about the existence of multiple personality disorder other than as a culture-specific or iatrogenic phenomenon. Many other conditions, such as neurasthenia, are reluctantly included. Disorders of the puerperium are only of use as estimates of workload on services. Simple schizophrenia, although included, is of unresolved status. Borderline personality disorder is hesitantly included and hyperkinetic disorder was broadened. Oppositional defiant disorder appears because of its predictiveness for later conduct disorder.

In *Neurasthenia*, or nervous debility/exhaustion, the sufferer complains of tiredness, depression, irritability, poor concentration, and *anhedonia*¹⁸² (also found in depression and schizophrenia), an inability to derive pleasure from anything. It commonly follows or is associated with exhaustion or an infection like influenza. Beard, an American described this syndrome, once attributed to overwork, in 1869. It has been argued that most cases of neurasthenia are actually cases of anxiety or depression. *Shenjing shuairuo*, in China, and *shinkeishitsu*, in Japan, are related concepts. Freud split off 'anxiety neurosis'¹⁸³ from Beard's neurasthenia in 1894. In 1909, Janet coined the term *psychasthenia* which was used to emphasise that the disorder was

¹⁸¹ Reflecting the 19th century concept of a 'unitary psychosis'.

¹⁸² **Disrupted in schizophrenia 1** (DISC1 at chromosome 1q) SNPs were studied by Tomppo ea (2009): Carriers of the minor allele of marker rs821577 had significantly higher scores on social anhedonia (ability to enjoy social interaction) in a Finnish population cohort study. The opposite applied to carriers of the minor allele of marker rs821633. Disruption in DISC1 in mice causes abnormal migration of neurones in the cerebral cortex.

¹⁸³ *Angstneurose*

psychological, not neurological.¹⁸⁴ *Hedonic tone* refers to the ability to experience pleasure, its absence meriting the label anhedonia¹⁸⁵. (Ribot, 1911; Snaith, 1992)

Personality disorders are deeply ingrained maladaptive patterns of behaviour that are generally recognisable in late childhood or early adulthood and with a not invariable tendency to diminish in intensity in the middle years; patient and/or society suffers as a result of it. Historically, Ernst Kretschmer and William Sheldon tried to associate so-called *somatotypes*, or body builds, with particular psychiatric conditions. There are three basic types, each one with overdevelopment of one of the primary embryonic layers: the endomorph with large visceral cavities and a tendency to bipolar affective disorder, the mesomorph with antisocial proclivities, and the ectomorph who has a tendency to develop schizophrenia. These are only of academic interest today, not having stood the test of time.

DSM-IV

There are five axes in DSM-IV. Kleinman (1988) wondered if its predecessors, DSM-III and –III-R, were guilty of a spurious numericalised specificity. Andreasen (2001, p.182) points out that DSM criteria may ‘limit creativity and flexibility’ in uncovering the pathophysiology of mental disorders. Cultural factors undoubtedly operate in the DSM system, e.g. multiple personality disorder (dissociative identity disorder) is largely an American diagnosis and many children diagnosed with attention deficit disorder in the US would attract a conduct disorder label on this side of the Atlantic.

DSM-IV definitions of psychosis

Delusions or prominent hallucinations without insight into their abnormality

Prominent hallucinations with insight into their hallucinatory nature

Other prominent symptoms of schizophrenia, such as disorganised speech, or grossly disorganised or catatonic behaviour

Impairment causing gross interference with capacity to meet ordinary demands of life

Loss of ego boundaries¹⁸⁶

Gross impairment of reality testing

The above serves to illustrate the lack of an all-embracing definition. This is well illustrated in DSM-IV’s varying use of the above definitions to emphasise different aspects of ‘schizophrenia and other psychotic disorders’.

DSM-IV Axes

Axis I: Clinical disorders and ‘other conditions that may be a focus of clinical attention’.

Axis II: Personality disorders and mental handicap (intellectual disability).

Axis III: Relevant (to understanding or managing mental disorder) general medical conditions – these are classified using ICD-9-CM¹⁸⁷ (clinically modified).

Axis IV: Psychosocial and environmental problems, such as relevant (to first two axes) domestic or economic problems.

Axis V: Global assessment of functioning (GAF) using the scale provided in DSM-IV.

Dress and address

Patients want doctors of both sexes to dress formally, the great majority prefer to address doctors by title, but they like to be called by their own first name or they may be undecided about this (Swift ea, 2000; Gallagher ea, 2008) – when in doubt, ask! In a study by Vinjamuri ea (2009) 91% of adult psychiatric outpatients across all age wished to be greeted with their first name¹⁸⁸; most wanted their hand to be shaken

¹⁸⁴ A French physician described **Briquet’s Syndrome** (St Louis Hysteria; now called somatisation disorder), a term rarely applied in Europe, in 1859. Classically, it occurs in women, starts before their thirtieth birthday, the patient persistently complains of a variety of physical symptoms, she will not accept a psychological explanation - even if one is obvious, and it is said to affect at least one in a hundred females. Sociopathic traits are not uncommonly associated with Briquet’s syndrome.

¹⁸⁵ A term introduced by Ribot in 1897.

¹⁸⁶ In psychoanalysis, the triumph of Id over Ego.

¹⁸⁷ The USA requires ICD-9-CM usage for coding purposes when billing for physical and psychiatric disorders.

¹⁸⁸ First and last names should be used initially for identification purposes.

and the doctor to introduced himself/herself as a doctor with their full name; and almost all patients wanted to know the doctor's role. This approach will require sensitive modification based on context, e.g. some Moslems males may not wish to shake hands with a female.

Management and prognosis

Preparation of a management plan should include investigations, immediate management strategies and long-term interventions; in each instance one should consider social, psychological and biological interventions, and ask who will intervene, when they will do it, and where will it be carried out.

We should consider both short-term (this episode) and long-term (recurrences/maintenance) prognoses; features of both illness and the individual with the disorder should be included in the discussion.(Holden, 1990b)

Case notes/progress notes

Avoid pejorative comments.(RCPsych, 1992) The Irish reader should note that it is UK Department of Health advice to send a copy of all correspondence about a patient between doctors to the patient.

Examples of offensive entries (Crichton ea, 1992)

Patronising
Stigmatising
Flippant
Pejorative lay terms

SOAP stands for subjective (from patient), objective, assessment, plan. This can be useful when highlighting a patient's care and dealing with a specific problem. Psychiatrists are in a very strong position to view clinical cases as a whole because of their commendable tendency to wade through the thickest charts in liaison settings.(Abbey, 1999)

Keeping records

Abbreviated draft MHC guidelines dated December 2007:

A major aim is continuity of care. Records should be completed contemporaneously with note taken of event and recording times on the 24 hour clock. Recording frequency must be sufficient to give an accurate picture of the patient at all times. Late entries should generally be avoided and, if essential, should not be squeezed into the record. Entries should not be predated. All healthcare professionals should be encouraged to read each other's entries when there is a need to know. Emphasis should be placed on a factual record: subjective comments should be avoided - if deemed necessary they should be explained. Do not alter, delete or destroy any original record. The record must provide evidence of care planning and provision. The record must be up to date, accurate and unambiguous. It should be written clearly and legibly. If the notes of others are unclear they should be asked to rewrite the record. Ensure that the record is permanent and capable of being photocopied. Avoid using initials. All entries must be signed off and the writer should be clearly identifiable by name and status.

Entries by students and assistants entries must be counter-signed. Maintain an up to date register of sample signatures. Keep the record in chronological order and explain any variance. Identify names and status of other involved healthcare professionals. Identify when other professionals were contacted and any advice given. Avoid abbreviations. Use only acceptable official grading systems. Record all advice give to the patient and record any decisions made. Be systematic by keeping all patients records together and having the patient's name and record number on every page of the record. Use care plans to assist. Seniors should supervise recording standards. Regularly audit the standards of records.

Writing prescription:

Accuracy, appropriateness, no ambiguity
Document advice including details of foreseeable/unforeseeable adverse events

Abbreviations:

Abbreviations should be kept to a minimum and only used in the context of care
References must be approved locally
Avoid in transfer/discharge contexts

Retrospective Notes:

Record date and time of entry and state date and time entry refers to

Narrative Case Notes:

Identify purpose of the notes and reflect the patient's legal status
Follow best practice – reflect before writing
Use short sentences with no unnecessary abbreviations
Use simple words where possible (quotes/observations are superior to jargon)
Be respectful, simple, direct, and specific
Be legible
Avoid generalisations
Avoid confusion/obscurity – be relevant, clear and objective

Distinguish facts from opinion
 Support ones professional opinions
 Describe treatment plan¹⁸⁹ and give classifiable diagnosis
 Make periodic reviews
 Place a line under the end of each entry

Professional Reports

Put title of case on front page
 Utilise a contents page with page numbers if report > 8 pages
 Identify author and purpose of report
 Give brief summary at beginning
 Clearly define issues being addressed
 Relevant background information/history
 State facts of the case as known to you
 Give information on examination/investigations carried out by you
 Give your professional opinion based on the facts and any published research, standards or guidelines available
 Give conclusions that summarises main points plus your opinion
 Distinguish between facts, information reported to you and your professional opinion
 Do not stray from your area of expertise
 Convey respect for patient
 Use simple, clear, plain language
 Explain any technical or medical terms if report is for layperson – may require a glossary
 Keep report as short as possible but include all relevant information
 Any published material referred to or consulted in preparing report should be included in appendices
 Re-read report and ensure you are satisfied with your conclusions
 Ask a colleague to read the report and comment on it
 Keep a copy on file

Discharge summaries are often deficient in the information required by GPs, especially regarding prognosis, mental state on discharge, management advice, and information given to patient and relatives.(Craddock & Craddock, 1990)

Electronic patient records (EPRs) may replace written records (which are sometimes unintelligible). One London survey (Mistry & Sauer, 2009) found that psychiatrists of various levels of experience (only 56% of consultants responded) experienced technical difficulties, confidentiality issues, extra workload and impact on clinical activity when using this system but that most would not return to using paper. Psychiatrists need administrative support and training if they are to adopt EPR successfully.

Clinical audit

This refers to the regular, systematic study and critical analysis of patient care by clinicians (Garden ea, 1989; Kelly, 2009), e.g. clinical *records* (random selection over a stated time period, e.g. acute admissions/unit time, or a subgroup of such files dealing with a specific problem, e.g. dementia; analysis of data, identification of record-keeping problems, examination of management practices, and recognition of need for further investigation), *incidents* (side-effects of drugs, ECT, admission or readmission rates, use of seclusion, etc), *criteria-based* (e.g. determine diagnostic criteria and standards of care for a particular diagnosis from discussion and the literature), and *outcome* (effectiveness of treatment from various points of view, symptoms, function, quality of life, mortality – use rating scales, interview schedules, etc.). Audit may also be classified as *external* (e.g. a training body determines subject), *department- or practice-based* (e.g. a department in the hospital collects and analyses the data on a subject of its own choosing), and *self-directed* (responsibility of a single clinician).

Clinical governance (quality control)

This continuing process aims to increase quality and reduce risk in clinical work. It should not be so rigid as to stifle practitioners. Essential components include evidence-based practice, good access to clinical information and other necessary knowledge, audit, checks on quality of practice and outcome, research, practice development, and adherence to guidelines.(James ea, 2005)

The *Medical Practitioners Act 2007* provides for competency testing (as distinct from knowledge recall) of doctors and has significant resource and time implications.(Nwachukwu, 2009) All doctors must be registered with a Professional Competence Scheme by May 1 2011. The College of Psychiatry of Ireland is assigned the responsibility of elaborating on the *competencies* required in psychiatry. A doctor must

¹⁸⁹ The *individual care and treatment plan* consists of recorded goals that were developed by the patient and his/her multidisciplinary team. The plan describes the treatment and support to be offered, the resources required, and the hoped-for outcomes.

demonstrate various skills (acquired by learning or practice), aptitudes, and performance levels. Examples of competencies are relating to patients, other interpersonal skills, collaboration and teamwork, management (including self-management), scholarship, professionalism, and clinical skills. Various approaches to assessment are possible, e.g. direct observation of practice, case-based assessment, written tests, audit against guidelines, case note review, and continuing professional development (CPD/CME).

Boundaries

Do not treat people you socialise or work with with (*dual-roling*) and ensure that a patient is formally referred.(RCPsych, 2007) Have a supervisor. It is unethical to engage in any sexual activity with current or former patients.Physical touch must be appropriate and not open to misinterpretation. Chaperones should be used when circumstances dictate that it would be safer to employ them. Family members¹⁹⁰ who speak a patient's language are poor substitutes for a neutral *translator* (see box) who will not interfere with the dynamics of the clinical interaction. Inappropriate self-disclosure must be avoided ('I remember when my husband left me....'). Avoid treating patients in your own home and treat in your workplace and during normal working hours when at all possible. Do not advise on matters that could be misconstrued (e.g. 'You would do well to see my brother who is a very good solicitor'.) or are outside your competence level. Do not break confidences.

Using translators

Avoid non-professional translators when possible¹⁹¹

Ask translator about aspects of patient's culture

Literal translations may be misunderstood

Re-phrasing and summarising of questions are often appropriate

Clinician should face the patient and address him/her instead of the translator

Allow patient to 'read' your body language

Give translator time to translate

Seek clarification if confused about answers or if body language and replies are incongruous

Avoid technical jargon

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¹⁹⁰ Family and carers may act as advocates for adult patients but they do not possess any automatic legal authority to make decisions on behalf of mentally ill or intellectually disabled relatives. The graver the decision the wider should the clinician consult and the final decision must always be in the **patient's** best interests and be the least restrictive alternative. Legally, an unwise or unconventional decision made by a patient does not mean that he/she lacks capacity.(see MHC, 2009)

¹⁹¹ **Translators:** Only use a friend/relative/clerical staff if you cannot avoid it. Relatives may talk for the patient instead of facilitating free expression by the patient. Relatives may attempt to change thought disorder into sensible language. Use of close others jeopardises confidentiality and may inhibit disclosure. Use trained interpreters who are fluent in the languages of therapist and patient and who will give literal translations and can with authority inform the therapist about the weight to be attached to beliefs about illness and use of metaphor in the patient's culture.

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2

Legislation & Ethics

Brian O'Shea

'Liberty is always unfinished business'. (American Civil Liberties Union, 1955-6)

Ethical principles governing Medicine and Law:

Ethics are the rules and standards governing conduct. *Ethics committees* provide essential safeguards. They examine the scientific value of proposed research, whether the study design is adequate to answer the hypothesis, and risk-benefit ratios of potential outcomes. They oversee matters such as informed consent¹⁹², adequacy of information given to participants, and subject protection (including insurance). Researchers must inform the committee should study parameters change. The Tuskegee, Alabama study of the 1930s prevented patients with syphilis from receiving treatment long after penicillin was discovered! (Pang, 2007)

*Deontology*¹⁹³ (Gk. *deon*, duty) is an ancient rule-based approach to moral questions: if a patient is in need of care then it should be satisfied by another person. *Teleology* (Gk. *teleon*, purpose), an outcome-based approach, became popular in the nineteenth century. In the former case, action is guided by rights and obligations without heed of outcome¹⁹⁴, whereas in the latter case the outcome¹⁹⁵ is crucial and action is aimed at doing what is best for the majority. In practice, neither of these approaches is of much assistance in daily clinical decision making. Instead, clinicians focus more on issues of respect for the autonomy of the patient (the patient's right to give/ withhold consent), doing good (beneficence: medical obligation to act in the patient's best interests¹⁹⁶) and avoiding doing harm (non-maleficence), and practicing in a just manner. (Gillon, 1994) There may be no single correct answer but rather a number of justifiable approaches to the index dilemma. (Roberts ea, 2008, p. 1608)

Other approaches to ethics include *virtue* (what a virtuous person would do), *relationship/care* (decisions based on commitments to others), *communitarian* (social values/traditions determine what is right), *casuistry* (details of the individual case/similar cases are the main basis for decision-making), and *principle-based* (based on doing good and not harm¹⁹⁷, respecting autonomy, and being just) ethics.

The practitioner must juggle a number of variables in order to act ethically and legally. Profound differences between Medicine and Law can sometimes give rise to poor communication and/or misunderstanding. (see Casey and Craven, 1999) The psychiatrist sees human action and disposition as the summed products of genetic, experiential, affective and cognitive inputs, whereas the lawyer assumes the presence of free will and responsibility. Whilst medical values governing acceptable action include

¹⁹² O'Donnell (2008, p. 12), a surgeon, writes: 'Now pre-operative options had to be fully explored and the acronym BRAT (benefits, risks and alternative treatments) became part of the surgeon's (and patient's) lexicon'.

¹⁹³ Associated with the German philosopher (Königsberg, now Kaliningrad) Immanuel Kant (1724-1804).

¹⁹⁴ *Kantianism* holds that telling the truth is almost always obligatory, regardless of the consequences (i.e. the strict Catholic teaching received by the author during the 1950-60s). In reality, this approach, if not tempered by common sense, could sometimes lead to disaster. Real life is often about striking a balance between competing needs.

¹⁹⁵ *Utilitarianism*, a consequentialist school of thought, is associated with the English jurist, philosopher and social reformer Jeremy Bentham (1748-1832) and the English philosopher, political economist and MP John Stuart Mill (1806-1873). Rigid utilitarian adherence would force some people to take an untried compound in the hope that the outcome might be positive for the majority.

¹⁹⁶ Best interest is difficult to define. Phil Fennell (2009), a law professor in Cardiff, suggests a balance sheet approach, i.e. a weighing up of advantages and disadvantages. We must listen to what the patient says and show unconditional positive regard.

¹⁹⁷ Beneficence and nonmaleficence respectively.

confidentiality, autonomy, and beneficence, the courts generally prefer legal principles, or systems of principles, to medical ethical systems. Exceptions occur when statements of principles have been incorporated into legislation, when Constitutional principles apply, or when the State has adopted international conventions.

The Irish Medical Council places a strict duty of confidentiality on medical practitioners. According to the Irish Medical Council (Medical Council, 2004, p. 29) lists four exceptions to confidentiality: when ordered by a Judge in a Court of Law, or by a tribunal established by an Act of the *Oireachtas*¹⁹⁸; when necessary to protect the interests of the patient, when necessary to protect the welfare of society, and when necessary to safeguard the welfare of another individual or patient. The ascertainment of information from third parties (e.g. relatives) is subject to the same rules of confidentiality: try to get the informed consent of the patient¹⁹⁹; relatives and friends do not have an automatic right to information.(Medical Council, 2004, p. 29) Medical information may be passed to another doctor who is caring for the patient, normally with the patient's knowledge and consent.(Medical Council, 2009) Recourse to the provisions of mental health legislation should be had in the case of psychiatric cases who are incompetent to give consent (a minority).(Medical Council, 2004, p. 30) *Tarasoff v Regents of the University of California*²⁰⁰, 1976, raises the ethical question of an obligation to disclose relevant information to a named potential victim of a patient.²⁰¹ The *Protection for Persons Reporting Child Abuse Act*, 1998, ('Shatter Act')²⁰² imposes an obligation on designated Health Board (now Health Services Executive) officers to report knowledge of any child who might be at risk of abuse.

The Protective Disclosures provisions of the *Health Act 2007* came into effect in March 2009. These provide protection against penalisation and civil liability for health service employees who disclose²⁰³ (in good faith and on reasonable grounds) matters about which they are concerned to an authorised person or regulatory authorities (or, in some circumstances, to other agencies such as the Health Information and Quality Authority [HIQA]).

Principles, Conventions and Protocols: All domestic legal interpretation must conform to the *Irish Constitution (Bunreacht na hEireann)*. Under it, the State's legislation must guarantee respect and defend/vindicate personal rights of the citizen. It must also protect citizens from unjust attack. In the case of injustice done, it must 'vindicate the life, person, good name and property rights of every citizen'. The right to bodily integrity followed from this in *Ryan v Attorney General*, 1963.²⁰⁴ Article 40.4.2 of the *Constitution* holds that one cannot be deprived of liberty except by proper recourse to law.

Principles and Covenant of the United Nations (UN): The *UN Universal Declaration of Human Rights* of 1948 is an influential, if not legally binding, document. Elaboration is provided by the *UN Covenant on Civil and Political Rights*. Everyone has a right to life, liberty and personal security; no one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment; no one shall be subjected without his/her freely given consent to medical/ scientific experimentation; everyone is entitled to a fair, equal, and public hearing by an independent and impartial tribunal, in the determination of his rights and obligations and of any criminal charge against him; no one shall be subjected to arbitrary arrest or

¹⁹⁸ Both houses of the legislature, i.e. Dáil and Senate.

¹⁹⁹ Children should receive as much information as they are likely to understand and their wishes should not be disregarded, but the practitioner 'must never assume that it is safe to ignore the parental/guardian interest'.(Medical Council, 2004, p. 32) Reports to an insurance company concerning a deceased person should only be issued with the permission of the next of kin or the executors to the estate.(Medical Council, 2004, p. 30) Reports of communicable diseases, in the absence of informed consent, should be to the relevant authority 'but should observe the patient's confidentiality in all other respects'.(Medical Council, 2004, p. 31) Likewise, if the patient refuses consent to disclosure of a risk of passing on a communicable disease to others, 'those who might be at risk of infection should be informed of the risk to themselves'.(Medical Council, 2004, p. 31)

²⁰⁰ In 1969 Prosenjit Poddar killed Tatiana Tarasoff. The Supreme Court of California ruled that mental health professionals have a duty to protect people threatened with physical harm by a patient.

²⁰¹ The important British case is *W v Egdell*, 1990: in the case of real risk of physical harm, confidentiality can be breached to those whom it is necessary to tell so as to protect the public interest. The Irish Medical Council guidance of 2009 affirmed its acceptance of the Tarasoff decision when it said that disclosure without a patient's permission could be done if failure to disclose placed others at risk of harm.(medicalcouncil.ie) Otherwise confidentiality should be maintained. In the presence of incapacity the clinician should consider what is in the patient's best interest.

²⁰² This Act raises questions relating to professional confidentiality, especially in an era of the multidisciplinary team.

²⁰³ I.e. whistle blowing.

²⁰⁴ This has been invoked in relation to prison conditions. It also has implications in relation to involuntary hospitalisation. The State has a duty to protect the health of persons held in custody as well as is reasonably possible in the circumstances: *State v Frawley*, 1978.

detention; no one shall be deprived of his liberty except on legal grounds; anyone who is arrested shall be informed at the time of his arrest of the reasons for the arrest and shall be promptly informed of any charges; anyone deprived of liberty by arrest or detention is entitled to take court proceedings so that the court may decide without delay on the lawfulness or otherwise of the detention; and anyone deprived of liberty should be treated with humanity and respect.

The 1991 *UN Principles for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care* states that everyone is entitled to good mental health care based on ethical rather than political/religious/cultural grounds, that they experience no discrimination because of mental illness, that community-based treatment be the standard, that the skills of mental health workers should not be used other than for the good of the patient, that medication is used for treatment purposes rather than to make life easy for deliverers of care, that voluntary patients should normally give informed consent for treatments and involuntary patients be kept informed about their treatment, that restraint/seclusion be governed by official guidelines, that mental health facilities be properly structured and receive appropriate resources, and that involuntary detention be re reviewed impartially in consultation with the responsible clinicians.

The WHO *World Health Report 2001: Mental Health: New Understanding, New Hope* advocated situating (and monitoring) mental health services predominantly in primary care settings/community, increasing availability of psychotropic drugs, educating the community and involving it/service users/families in care delivery, that mental health national policies/programmes/legislation be developed with appropriate resourcing, that links be forged with other services, and that research into mental health/related issues be supported.

The *UN International Convention on the Elimination of all Forms of Racial Discrimination* of 1963 places an obligation on States to prohibit and to eliminate racial discrimination and to guarantee the rights of everyone, without distinction. This Convention includes medical care as a right.

Europe: The *European Convention for the Protection of Human Rights and Fundamental Freedoms* of 1950 precludes the use of torture or degrading treatment or punishment. Everyone has the right to liberty and security of person. No one shall be deprived of his liberty save in stated circumstances.²⁰⁵ In 1987, the Council of Europe established the *European Convention for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment* to allow for inspection of prisoners and psychiatric inpatients. The *Convention on Human Rights and Biomedicine* of 1997 provides that the dignity²⁰⁶ and identity of all persons shall be protected. Everyone is guaranteed equal respect for their integrity and human rights and fundamental freedoms with regard to the application of biology and medicine. Individual interests and welfare predominate over the sole interest of society or science. Appropriate measures must be taken to provide equitable access to appropriate health care. Any intervention in the health field, including research, must be carried out in accordance with relevant professional obligations and standards. Subject to protective conditions prescribed by law, a person who has a serious mental disorder may be subjected, without his or her consent, to an intervention aimed at treating his or her mental disorder only when it would entail serious harm to the person's health not to intervene. Emergency treatment without appropriate consent is allowed in an emergency. Article 9 says that previously expressed wishes shall be taken into account for those persons not (at the moment of the intervention) in a state to express his/her wishes. The *European Convention on Human Rights Act 2003* applies to Ireland subject to the provisions of the Constitution. It can be traced back to New Zealand's Bill of Rights Act 1990 which states that domestic law must provide those fundamental rights guaranteed by international law. Public bodies must adhere to the relevant fundamental rights unless blocked from doing so by statute law and the latter must be viewed in terms of such fundamental rights when such interpretation can be reached. Courts have this obligation to take 'due account' of the *Convention*.

²⁰⁵ I.e. lawful detention of persons for the prevention of spread of infectious diseases, of persons of unsound mind, alcoholics or drug addicts, or vagrants and in accordance with a procedure prescribed by law; and the lawful arrest or detention of a person for non-compliance with the lawful order of a court or in order to secure the fulfilment of any obligation prescribed by law. Zigmond (2009) is critical of the lumping of psychiatric patients together with vagrants, addicts, and so on.

²⁰⁶ One definition of dignity is the right to be treated with respect as a separate individual.

Domestic legislation: The major piece of legislation in Ireland up to 2006 was the Mental Treatment Act, 1945.²⁰⁷ Mental Health legislation can be confusing and the best way to gain an understanding of it is to read the various Acts in the original. The Mental Health Act, 2001 was introduced in 2006.

The Mental Treatment Act 1945 (Ireland²⁰⁸) covered many aspects of the workings of the psychiatric service and not just those concerned with the welfare of patients.

Section 12 in Part II established the post of Inspector of Mental Hospitals, a post with wide ranging powers. He had to inspect all hospitals in the State at least once per year²⁰⁹. He was allowed to examine all aspects of management of these institutions and also interview patients. He reported to the Minister on his findings. The Inspector could examine any hospital at anytime and he also had the power to examine employees on oath (Section 242). It was an offence to obstruct the Inspector of Mental Hospitals in his duties.(Section 279) Part XIV was concerned with 'Reception Orders'. There was the Person of Unsound Mind (PUM) Order, which was very restrictive as regards patients' rights, but it was an Order that had been allowed to fall into abeyance despite the fact that it was the only Order that that could be used to procure a police escort.²¹⁰

Temporary Committal Orders²¹¹ were covered in Part XIV (Sections 184-189). The private temporary order required two doctors' signatures²¹² rather than the one required in the case in the public patient order. Both orders allowed for the compulsory detention of a person suffering from a mental illness or an addiction. Voluntary admissions were covered by Section 190 and the 72-hour notice regulation (giving notice of self-discharge) was covered by Section 194. Section 207 was concerned with the transfer of detained patients to the Central Mental Hospital²¹³. This provision was deemed unconstitutional and had been replaced in practice by Section 208 which basically involved procuring agreement between the Clinical Directors of both the referring service and the Central Mental Hospital.

*The Mental Health Act, 2001*²¹⁴ is a product of concern over civil liberties (Mills, 2001) and resources.(Cassidy, 2003; Ní Mhaoláin & Kelly, 2009) (Before the 2001 Act a patient had no automatic right to review of his/her detention and the single route of challenge was an application to the High Court (*habeas corpus*) under Article 40.4 of the Irish Constitution.) A Mental Health Commission (to oversee the Act), Tribunals²¹⁵ (to check on involuntary admissions) and an Inspector of Mental Services²¹⁶ are provided for. Tribunals are composed of one practising barrister or solicitor (in the Chair), one consultant psychiatrist, and a person other than from the foregoing categories (not a registered doctor or nurse).

Mental Health Act, 2001

Concerned with involuntary admissions (O'Shea, 2002a; Kelly, 2007)

Definition of 'mental disorder' (S.3) is paraphrased in next box

Best interests of the patient must be upheld

²⁰⁷ *The Health (Mental Services) Act, 1981* was passed by all the Houses of the Oireachtas but was not signed into law. One criticism of the Act is that it proposed that all committal orders to hospital would require two General Practitioners' signatures. Information concerning the names of patients in a hospital and also copies of their reception orders could be made available to 'any person' who 'may apply to a Health Board for information' and Section 34 required that the Medical Officer provide copies of the various documents to the detained patient! Psychiatric review boards were to be established.

²⁰⁸ 19 Parts and 284 Sections. S 260 stated that the patient could not bring a case challenging committal to Court without the leave of the High Court – the latter had to be satisfied that there were substantial grounds for contending that the defendants acted in bad faith or without reasonable care. S 260 was found to be unconstitutional on December 7 2004 (in the *Louis Belenheim v St John of God Hospital* case) by the High Court (see articles 6 and 34 of the Constitution). On appeal, the Supreme Court upheld the decision of the High Court: (2008) IESC 40.

²⁰⁹ Twice a year for private institutions.

²¹⁰ The Order stated that the patient was unlikely to improve in less than 6 months. The Clinical Director could ask a PUM patient to sign a Voluntary Form, so negating the PUM.

²¹¹ Private and public; patient likely to improve in less than 6 months.

²¹² Originally meant to protect private patients who may have some wealth.

²¹³ Evidence had to be given to a Justice of the District Court that the patient has committed an indictable offence; the Justice had to be satisfied that the person would be unfit to plead if he were to stand trial and he makes an order for the transfer; the Inspector of Mental Hospitals then made a report to the Minister who, in turn, could complete the order for the transfer.

²¹⁴ 6 Parts & 75 Sections.

²¹⁵ Prof Terry Carney (2009), a law professor, provided some interesting contrasts between Irish and Australian (respectively) mental health tribunals (MHTs): time before hearing 3 v 8 weeks; duration hours v 20 minutes; revocations 10% v about 2%. Australian patients complain that MHTs are trial-like, disempowering and tend to exclude the 'consumer' (patient) and the setting may be off-putting (a round table is superior to 'sides' ranged either side of a long table). He feels that a case conference model should be adopted with the patient fully involved and that the medical (rational treatment) and social (e.g. concerns over property, rent payment, etc) domains should be seen as more important than the legal domain.

²¹⁶ Formerly Inspector of Mental Hospitals; must visit mental health services on a yearly basis and can take evidence under oath.

Admission under S.3.1.a is because of a danger posed by the patient (because of an abnormal mental state) to self and/or others

Admission under S.3.1.b must be likely to alleviate or benefit the patient 'to a material extent'

Patient must be kept reasonably informed of what is going on (admission, treatment)

Personality disorder, social deviance, and substance abuse not grounds for involuntary admission *per se*²¹⁷

Gardai²¹⁸ can enter premises by force to make contact with a patient they have serious concerns about

Gardai can be requested to provide an escort in order to get (detainable) patient to an approved centre

Certain officers of health boards, among others, are authorised to act as applicants²¹⁹

'Spouse' does not include someone living apart from the patient or on who is the subject of an application under the *Domestic Violence Act, 1996*

A registered medical practitioner makes a 'recommendation' for involuntary admission of the patient

There is no provision under the Act to transfer an involuntary patient abroad

A Mental Health Tribunal can 'cure' minor irregularities (e.g. minor mistake in date) in the paperwork under S 18(1) as long as it is in the patient's best interests to do so and as long as no injustice was done as a result of the irregularity but the Tribunal cannot bend the law to the degree that 'violence' is done 'to the words of the Act itself'

Where the patient's legal representative is unable to get the patient's competent permission to read his file such permission may be granted by the sitting Tribunal or by 'the hospital or treating psychiatrist therein' (EJW case, Peart J, November 2008)²²⁰

What is a voluntary patient? In the EH case²²¹ (Supreme Court, May 2009) he/she was defined as someone who is receiving care and treatment in an approved centre who is *not the subject of an admission order or a renewal order*. He/she is **not** defined as a person who freely and willingly gives consent to an admission order. (Madden, 2009)

Standard of proof required at Mental Health Tribunal

'...to a standard of a high level of likelihood as distinct from simply being more likely to be true'. (MR, High Court, 2007)

This falls short of 'beyond a reasonable doubt'.

Likelihood of physical and/or mental harm occurring must be regarded as 'immediate'.

A minor injury to the self does not qualify as being 'serious' whereas the same injury to a third party would qualify.

The Commission must be informed of all involuntary admissions. Patients must be given a written statement of their rights (S.16(2)). The Commission will refer the case to a Tribunal who will review the case and either affirm or revoke the admission order. The tribunal can discharge the patient, allow the

²¹⁷ 14% of involuntary admissions in 2002 had personality disorder, alcohol disorders, or drug dependence, all of which are excluded *as such* as grounds for detention under the 2001 Act.

²¹⁸ **Garda** (police) involvement under the 2001 Act: as an applicant in the involuntary admission process (s. 9), taking a person into custody because there is a serious likelihood of immediate and serious harm to self/others (s. 12), assisting in removal of patient to approved centre (s. 13), and returning an involuntary patient to approved centre (s. 27). From a police perspective the major gap in services is the lack of a facility to which a Gard can take a person in crisis regardless of diagnosis without being asked to take the person away again. Such a centre would help the person to calm down and prevent escalation of the crisis. A number of models of police-mental health service crisis intervention cooperation have been reported such as the Specialised Police Crisis Intervention Team in Memphis Tennessee. (MHC & An Gardaí Síochána, 2009) Whatever model is adopted it should be modified according to local needs and resources and adequate training and consultation are mandatory requirements. Selection of Gardaí as crisis intervention personnel should be based on personal attributes such as a calm disposition and a flexible approach to problems. Court diversion schemes to prevent unnecessary criminalisation of mentally ill people who commit petty crimes are another area worthy development.

²¹⁹ There were 1,503 applications for involuntary admission of adults reported to the MHC in 2007. Applications were made by spouse/relative (69%), Gardai (15%), 'any other person' (9%), and authorised officer (7%).

²²⁰ This makes practical and ethical sense. The author's practice under the 1945 Act was that he gave permission to a legal representative **of the patient** to his in-patient client and any documentation that was relevant. If the patient lacked capacity and there was any reason to suggest that the legal representative represented other interested parties and if I had any doubt in my mind I would firstly refer the matter to the legal advisors of my employer and/or the Medical Protection Society.

²²¹ In the same case the Supreme Court stated that appeals to the Courts based on a defect in an earlier period of detention should only occur when there was a gross abuse of power or where fundamental requirements were not met.

admission order to run its course, or extend the order by periods of 14 days.²²² A patient (or solicitor²²³) can appeal the findings of a Tribunal to the Circuit Court. This must be in writing and within 14 days of receipt of the findings/decision. A medical or nursing member of staff can hold a voluntary patient for up to 24 hours if deemed necessary (S.23), at which case the responsible consultant psychiatrist (RCP: one who is involved in the care and treatment of the patient²²⁴) can either discharge the patient or arrange for a second consultant opinion (S.24)²²⁵. The fact that a patient must indicate a wish to leave the approved centre before S. 23 can be used makes little clinical sense²²⁶. The Health Services Executive (HSE) can apply to the District Court²²⁷ for authorisation to detain a child.(MHC, 2006)

Admission orders last initially last for 21 days and can be renewed for up to 3 months; they can then be renewed for up to 6 months and thereafter for periods of up to 12 months²²⁸ at a time.

The time that the Renewal Order commences was addressed by the High Court and thereafter by the Supreme Court case of *MD -v- St. Brendan's Hospital, MHC, MHT* of 27 July 2007. That decision confirmed that a Renewal Order takes effect on the expiration of the previous Order and not the date on which the Order is signed. A Tribunal's decision concerning an admission must be made within 21 days²²⁹. If a defect in an Order is not complained of at the relevant Tribunal it cannot subsequently be used in argument at a later Tribunal. Under the Act, an involuntary person suffering from a mental disorder who has been admitted to an approved centre shall *not* be a participant in a clinical trial. Bodily restraint and seclusion are subject to rules made by the Commission.

The treating psychiatrist should normally ensure that his/her patients give free and informed consent to treatment. However, treatment can be given without consent if the patient is incapable of giving consent. Psychosurgery²³⁰ requires written consent from the patient and authorisation from a Tribunal. ECT requires written consent from the patient and the agreement of two consultant psychiatrists, one being the treating consultant. Following 3 consecutive months of drug therapy, written consent from the patient for further such treatment is required, or such treatment can be authorised by 2 consultant psychiatrists, one being the treating consultant (3-monthly renewal thereafter).

Mental Health Act, 2001

(a) *Definition of 'mental disorder'*: mental illness (abnormal thinking, perceiving, emotions, or judgement seriously impair mental function and necessitating intervention for sake of self and/or others), severe dementia (intellectual, psychotic, and behavioural manifestations) or significant intellectual disability where²³¹ –

1. Person very likely to cause immediate and serious harm to self or others
2. Judgement is so impaired that without admission significant deterioration is likely or appropriate treatment would not be possible
3. Admission would materially help the patient or alleviate the disorder

²²² Such an adjournment extends the review of the existing Order **but not the life of the Order**: the responsible consultant must still complete an Extension Order in order to hold the patient in the approved centre.

²²³ Interestingly, the independent psychiatrist (S. 17) may read the patient's medical file but the legal representative requires the patient's permission! Where the latter is not forthcoming permission has to be sought from the Tribunal.

²²⁴ Sometimes this can mean that there is more than one RCP and any of these can make a renewal order. (JB(2) 2007, unreported) A locum consultant can be the RCP. The important issues at tribunals are (a) the RCP knows the patient and his/her history and (b) is involved in the care and treatment of the patient, i.e. the psychiatrist has more than a 'peripheral' involvement in the case. If a consultant takes over from the usual RCP 'once his shift has started he was the person to whom those working under him would refer matters on which they needed advice or consultation' (JH case): i.e. the Courts are aware that RCPs get sick, have rotas, take holidays, etc. WQ case: a psychiatrist not attached to the approved centre and not involved in the care and treatment of the patient cannot make a renewal order.

²²⁵ S.24 cannot proceed unless S.23 has first been applied to the voluntary in-patient.

²²⁶ What happens to the patient with catatonic mutism who will not eat or the psychotic patient who lies in bed and will not take treatment but who nonetheless do not indicate a wish to/try to abscond?

²²⁷ In late 2009 the Law Reform Commission suggested that persons admitted and treated under the 2001 Act should have access to an independent advocate and a mental health tribunal (rather than the District Court) should review their admission and treatment.

²²⁸ The *exact date* of termination of this renewal order must be stated on the relevant form.

²²⁹ The first 'legal day' is not necessarily 24 hours long as it end at midnight on the first day of completion of a detention order.

²³⁰ In the *Mental Health Act, 2001* (s. 58) **psychosurgery** is any 'surgical operation that destroys brain tissue or the functioning of brain tissue and which is performed for the purposes of ameliorating a mental disorder'.

²³¹ Any number of these 3 can be used according to a High Court decision, not simply either or as initially stated.

(b) *Time limits under the Act*–

1. Applicant must have seen subject not more than 48 hours before applying
2. Doctor making recommendation must examine patient within 24 hours of receiving application
3. Recommendation remains valid for 7 days
4. Decision to detain at approved centre to be made within 24 hours (was 72 hours in the 1945 Act)

*The Mental Health Act, 2008*²³² was rushed through the Dáil at the end of October 2008 because extensions of detention as stated on Form 7 (renewals) were deemed to be too imprecise (e.g. a full 12 months might not be required to treat the patient). Henceforth precise periods with termination dates are required.

Mental health tribunals during 2008

Cost for tribunals €9,755,433 (per notification €2,922)

2,004 involuntary admissions, 2,096 hearings (241 revocations at hearings)

1,324 renewal orders

1,290 orders revoked by psychiatrists before tribunal hearings

Findings of a postal survey of 238 consultant psychiatrists in Republic of Ireland (O'Donoghue & Moran, 2009)

Subject: experiences and attitudes post-Mental Health Act 2001 introduction

70% response rate

48% felt care of voluntary patients deteriorated

32% felt care of involuntary patients improved

69% stated involuntary patient status was being changed to avoid a tribunal

14% re-admit patients involuntarily just after a tribunal revocation

57% of placements saw reduced training of junior doctors

87% report increase in on-call service workload

23% report increase in service consultant complement

A majority worry about not admitting patients with personality disorders or substance abuse *per se* as involuntary patients

Waterford Mental Health Services November 2006-October 2009 (Umedi ea, 2010)

2,254 admissions (130 or 5.8% involuntary from outset)

66 (51%) of involuntary admission orders revoked by treating consultant

64 (49%) of involuntary admission orders reviewed by mental health tribunal (MHT)

Of those reviewed by MHT: 87.5% affirmed and 8 (12.5%) revoked

Revocations were all on grounds other than absence of a mental disorder, e.g. recommendation preceded application

National survey of 735 MRCPsych holders²³³ in Ireland (Jabbar ea, 2010)

Examined views 1 year after full implementation of the Act

Respondents views (only 43.7% response rate):

Satisfied with training – 84%

Increase in workload – 69.1%

Reduced time with service users – 26.8%

Changed relationship with service users – 40.7%²³⁴

Did not believe Act could be implemented – 27.4%

Other issues: adversarial tribunals, effects on doctor-patient relationship, and issues regarding minors

The Criminal Law (Insanity) Act 2006, (Cassidy, 2003; Wrigley, 2003; Barry, 2006; Kennedy, 2007) became law in 2006. If a judge finds the defendant unfit to plead he may issue a hospital & treatment order

²³² A woman (SM) who had been admitted to St Patrick's Hospital in Dublin challenged her detention in the High Court stating that she was being detained because of lack of suitable accommodation outside hospital. Her legal team stated that the period of renewal was too imprecise: 'not in excess of 12 months'. The judge found that she was not well enough to leave hospital. In response, a new Form 7 was created by the MHC. Cummings and O'Connor (2009) suggest that the direct costs of the case (€993,377) could have provided supported accommodation for SM for 37 years!

²³³ This group includes senior and junior psychiatrists. Consultants were most likely to report negative views.

²³⁴ Some said they were more empathic but others that legalism had crept into the relationship with resultant conflict.

(with independent reviews) or a community order. The Act introduced diminished responsibility and (re-)introduced the verdict of 'not guilty by reason of insanity' into Irish law. The Minister designates psychiatric centres to receive persons diverted from the courts. Lack of secure facilities in non-forensic settings is worrisome. (O'Shea, 2002; Brophy, 2003) Interaction between the *Criminal Law (Insanity) Act 2006* and the *Mental Health Act, 2001* requires further consideration in order to avoid disrupting care of patients. (MHC, 2008, p. 83)

Part II of the Irish *Powers of Attorney Act 1996* allows a person to make an enduring power of attorney. The donor gives an attorney power to make personal welfare decisions on his/her behalf: such power has to be in a form prescribed by the Minister for Justice, the attorney must apply for the power to be registered with the Office of Wards of Court when the donor is/is becoming mentally incapable, certain people must be notified of the intention to register such power, and there are certain grounds for upholding objections to registration.

UK:

Mental Health Act 2007 (Zigmond, 2008) for England and Wales²³⁵, as of November 2008²³⁶ introduced community treatment orders (CTO)²³⁷. Children cannot be put on adult wards²³⁸. Non-medical

²³⁵²³⁶²³⁷²³⁸ **The Mental Health Act 2007** amends the the *Mental Health Act, 1983* and the *Mental Capacity Act 2005*.

Mental Capacity Act 2005 in England and Wales, (Jones, 2005; Church & Watts, 2007; Church & Jones, 2008; Nicholson ea, 2008) states that a person lacks capacity if at a relevant time he is unable to decide in relation to a particular matter due to an impairment/disturbance of mind/brain. The Act applies to carers and professionals. People with capacity can appoint others to make decisions for them if/when capacity is lost (lasting power of attorney). They can also state what treatments they would wish to refuse should they become incapacitated in the future (advance directives). Should a person lose capacity without having appointed a lasting power of attorney, the Court of Protection may be involved in deciding on capacity and in handling financial/health/welfare decisions. Doctors are able to make decisions based on the Act and will not have to rely on common law.

Principles of Mental Capacity Act 2005, England and Wales (Bartlett, 2006)

A person is presumed to have capacity if there is no evidence to the contrary
 A person does not lack capacity just because of an unwise decision
 Decisions made on a person's behalf must be made in his/her best interests
 Such decisions should intrude as little as possible into rights/freedom of action
 A person must be helped to make a decision before he/she can be treated as lacking capacity

The Mental Health Act, 1983 (England & Wales) replaced the *Mental Health Act 1959* and was itself amended in 2008. 10 Parts in the Act and 149 Sections. Many experts felt that it erred too much on the side of rights to freedom as distinct from rights to treatment ('Rotting with your rights on'). It attempted to continue the philosophy of community psychiatry. Nevertheless, it was followed by almost doubling of the numbers of compulsory admissions during first 12 years of its existence (Wall ea, 1999)

Part I dealt with definitions of mental disorder, severe mental impairment, mental impairment and psychopathic disorders. There was no definition of mental illness! Promiscuity, sexual deviancy and dependence on drugs or alcohol excluded as categories for compulsory detention in hospital

Part II concerned with compulsory admissions to hospital and also guardianship. Guardianship is not commonly used in practice, perhaps because of resource implications. (Taylor & Estroff, 2003, p. 607) Provision for admission for assessment (S2) admission for treatment (S3) and emergency admissions (S4) S. 5 (2) allowed detention of an inpatient (incl. in a general hospital) for up to 72 hours – this allowed a fuller section to be completed

S. 5 (4) allowed a nurse to detain a patient for up to 6 hours for a detention process to begin

S. 12 described requirements for 'approved doctors'

S. 114 lays down regulations for 'approved social workers' - approved social workers central to workings of Act and provide the vast majority of the 'applications'

Part III concerned with the mentally abnormal offender: courts can make orders for treatment and assessment of people on remand

S. 37 was a Hospital Order - allowed court to commit person to hospital for treatment instead of sentencing

S. 41 concerned with Restriction Orders - here a higher court could put a restriction on discharge of a patient who is committed to hospital on a Hospital Order - patient cannot be discharged without the permission of the Home Secretary. Court must hear oral evidence from a psychiatrist before making a Restriction Order

Part IV provided regulations concerning a patient's consent to treatment. If a detained patient does not want treatment, including medications, after 3 months one must arrange for a second opinion. Special treatments such as ECT and psychosurgery have greater restrictions

Part V concerned with mental health review tribunals that review detained patients annually if requested to do so by the patient. They must review detained patients every 3 years. They have various powers depending on the category of detention.

S. 136 concerned powers of police who encounter a mentally disordered person in a public place. They could take the person to a 'place of safety'

Section 136 facilities are inadequately developed so that many patients are detained in police custody. (Anonymous, 2008)

²³⁷ Such orders only apply to patients detained in hospital for treatment. The responsible clinician may discharge such a patient under a renewable supervised CTO which may specify conditions, including treatment compliance. Discharge from a CTO is only via the responsible clinician or a mental health tribunal. The patient can be recalled to hospital if deterioration occurs or certain conditions are not kept. Medication can only be given forcibly within hospital.

professionals may take overall charge of patients' care and treatment²³⁹ and provide the report required to renew detention orders.²⁴⁰

Mental Health Act 2007 – main provisions

Single definition of 'mental disorder'²⁴¹

Statutory advocates for detained patients

Under-18s must be accommodated in age-appropriate setting

'Appropriate medical treatment test' applies to all longer term detention powers

Medical treatment must be available and appropriate

'Treatability test' abolished

Broadens group of practitioners²⁴² who taken on functions formerly held by Approved Social Workers and Responsible Medical Officers

Patient can apply to have nearest relative displaced²⁴³; nearest relative can now include civil partners

Single Mental Health Review Tribunal and shorter period before cases are referred to it by hospital managers

New safeguards for electroconvulsive therapy²⁴⁴

Supervised community treatment following detention

'Bournewood safeguards' for non-detained persons who lack capacity²⁴⁵ – legal safeguards, no arbitrary decisions, powers of challenge

Mental Health Act 2007 – important sections

2 – Assessment & treatment (lasts 28 days): signed by 2 doctors or 'approved clinicians' + nearest relative or approved mental health worker

3 – Treatment (6 months): signed by same as s2

4 – Emergency admission (72 hours): signed by 1 doctor or 'approved clinician' + relative or approved mental health worker

5(2) – Emergency detention of inpatient (72 hours): signed by doctor in charge of case or nominee or approved clinician

5(4) – as for 5(2) (6 hours): signed by registered mental nurse

136 – Police bring patient to hospital because person in public place thought to have mental illness + need place of safety (72 hours): signed by police officer

²³⁸ In mid-2009 the MHC, in response to continued admission of children to adult approved units issued an **Amendment to: Code of Practice Relating to the Admission of Children under the Mental Health Act 2001**: MHC will review the number of admissions of children to approved centres for adults from time to time. In respect of the admission of a child to an approved centre for adults, the following applies: no child under 16 years is to be admitted to an adult unit in an approved centre from 1st July 2009; no child under 17 years is to be admitted to an adult unit in an approved centre from 1st December 2010; and no child under 18 years is to be admitted to an adult unit in an approved centre from 1st December 2011.

If, in exceptional circumstances, the admission of a child to an adult unit in an approved centre occurs in contravention of the above, the approved centre is obliged to submit a detailed report to the MHC outlining why the admission has taken place. This report should be in the form specified by the MHC as per Section B of the *Notification to the Mental Health Commission of the admission of a child to an adult unit in an approved centre*. **Section 2.5m** is amended to read as follows: MHC should be notified of all children admitted to an approved centre for adults within 72 hours of admission and also notified of the discharge of all children from an approved centre for adults within 72 hours of discharge using the associated clinical practice forms. Procedures should be in place to identify the person responsible for notifying the MHC.

²³⁹ Hence one doesn't have to be a psychiatrist to be the 'responsible clinician'.

²⁴⁰ A large majority of Irish patients who had been the subject of involuntary detention in a private psychiatric hospital were interested in having the option of an *advance directive*. (O'Donoghue ea, 2010)

²⁴¹ Replaces the 1983 four definitions of mental disorder, severe mental impairment, mental impairment and psychopathic disorders.

²⁴² 'Approved Mental Health Practitioners' (social workers, mental health or learning disability nurses, occupational therapists, and chartered psychologists) and 'Responsible Clinicians' (registered medical practitioners and Approved Mental Health Practitioners). When a patient on a **Community Treatment Order (CTO)** is returned to hospital, the Responsible Clinician has 3 days in which to decide whether to send the patient out on a CTO or to revoke the Order, i.e. to keep the patient in hospital, but the Responsible Clinician must have the agreement of an Approved Mental Health Practitioner. Hall and Ali (2009) expressed concerns about the changes in the Responsible Clinician role and about the effect this might have on relationships between professions as well as on the role of the psychiatrist.

²⁴³ A relative can be displaced by County Courts if reasonable to do so.

²⁴⁴ ECT cannot be given to a person who has capacity unless in an emergency, i.e. to save the person's life or to prevent serious deterioration in his/her condition. A 'Second Opinion Doctor' has to examine the patient. Parental permission does not override the decision of patients aged 16-17 who have capacity.

²⁴⁵ See 'Bournewood gap'.

*Mental Health (Care and Treatment)(Scotland) Act 2003*²⁴⁶ was passed in early 2003, replacing the *Mental Health (Scotland) Act 1984*. Whilst treatment cannot be forced on a person in his/her own home, that person may be removed to a specified place for 6 hours so that treatment may be administered. (Lyons, 2008) 'Advance statements' are written statements setting out how the patients wants to be treated for psychiatric illness should mental disorder impair their decision-making ability. (Foy ea, 2007) A study of psychiatrists' views and experiences (76% response rate) showed that 12% believed it improved patient care but most respondents believed that informal patient care had suffered, that tribunals were no better than the previous court system, and that out-of-hours work had increased. (Carswell ea, 2007) However, satisfaction with the Act among psychiatrists may have improved with time. (Donaldson ea, 2008) According to Owen ea (2008), mental capacity to make treatment decisions is usual in detained patients and common in voluntary in-patients. Owen ea (2009a) examined consecutive admissions²⁴⁷ to a London psychiatric hospital (Maudsley) and found that psychotic disorders and the manic phase of bipolar affective disorder were most strongly associated with lack of capacity; in non-psychotic cases, unlike in psychosis, depressed mood was associated with capacity status; insight was the best discriminator of capacity status in psychosis and mania but is less discriminating in non-psychotic cases; and cognitive performance did not predict capacity status in cases with psychosis. In a further publication, Owen ea (2009b) examined 200 psychiatric inpatients using the *MacArthur Competence Assessment Tool for Treatment*: a quarter were informal (voluntary) but lacked capacity and these people felt more coerced and were more likely to refuse treatment than voluntary patients with capacity; a small number of detained (involuntary) cases had capacity and were difficult to characterise. *Adults with Incapacity (Scotland) Act 2000* establishes statutory authority to treat adults who are not able to consent for themselves. A proposed treatment must be for the patient's benefit; it must be the least restrictive intervention; account must be taken of known/present wishes (if available); consultation should take place with family/carers/appointed proxy; and the patient should be helped to exercise any remaining capacity.

Incapacity in Northern Ireland

Covered by *Mental Health (Northern Ireland) Order 1986* Part VIII and *Enduring Powers of Attorney (Northern Ireland) Order 1987*

Management of the patient's affairs are controlled by High Court via Office of Care and Protection – a controller is appointed to manage patient's finances

Northern Ireland intends to introduce an Act that covers both capacity and mental health

Fitzpatrick & Anor v K. & Anor (2008) IEHC 104 (Irish High Court)

A female Jehovah's Witness (K) booked into Coombe Hospital Dublin as a Catholic

She bore a baby boy in September 2006

She suffered a postpartum haemorrhage but refused blood transfusion

An emergency High Court order allowed the hospital to give the transfusion

The hospital sought (at the court's behest) a declaration that it was entitled to seek the order

Principles involved in determining capacity re-stated by court:

Adults have capacity to refuse treatment, but this is a rebuttable presumption

Cognitive ability has to be so impaired that patient doesn't sufficiently understand the nature, purpose and effect of the treatment and the consequences of accepting/rejecting it in light of all available choices

Cognitive ability is so impaired that patient is incapable of making the decision to refuse because he/she does not understand and retain²⁴⁸ the information about the treatment and consequences likely to follow refusal; does not believe the information given (especially that death is a likely outcome); has not weighed the information, alternative choices and likely outcomes 'in the balance' in arriving at his/her decision

The doctor must tell the patient about the appropriate treatment, its risks/consequences, and available choices

²⁴⁶ The *Mental Health (Northern Ireland) Order, 2004* applies in Northern Ireland.

²⁴⁷ 200 patients participated but 150 did not participate. Dysfunction on the GAF was similar in both groups. Decision making was measured with the *MacArthur Competence Assessment Tool for Treatment*. (Grisso ea, 1997)

²⁴⁸ Retention of information need only be brief. (Lush, 2008, p. 770)

The doctor must recognise/note if misunderstanding/misperception of the information might represent lack of capacity

Irrational decision or decision made for irrational reasons is NOT relevant to the assessment

Regard must be had to the gravity of the decision and the likely consequences

Incapacity in the Republic of Ireland

Wardship (Ward of Court): Wardship is a practice of uncertain antiquity. It was originally exercised by the Court of Exchequer, later passing to the Lord Chancellor, and now lies with the President of the High Court under *Lunacy Regulation (Ireland) Act 1871*. (see Agyapong & Wrigley, 2009) Application (usually by a relative with two supporting medical affidavits) may be made to have the court appoint a representative to manage the affairs and provide for the welfare of a mentally incapacitated person²⁴⁹ (e.g. dementia). It is important to note that wards of court are not subject to the 'reception, detention and treatment regime' of mental health legislation. (O'Neill, 2004, p. 119) It is also important to note that medical interventions in such cases require the permission of the High Court. However, emergency interventions are allowed, permission being retrospectively sought (via The Office of Wards of Court²⁵⁰) as soon as is feasible. The Irish Medical Council (medicalcouncil.ie) states that if a patient with disability lacks capacity the clinician should consult parents/guardians/carers and, when relevant, consider getting a second opinion.

Irish Mental Capacity Bill 2008²⁵¹

Designed to replace Wards of Court

Only applies to adults

Evidence level – balance of probabilities

Capacity is the ability to understand nature/consequences of a decision in context of available choices at time decision has to be made

Lack of capacity signified by inability to understand/retain/weigh information relevant to the decision or to communicate decision – must be tested for in relation to the decision in question

Doctor's overriding duty – act in patient's best interests

Must presume capacity is present (even if person makes unwise decisions); intervene only if necessary in particular circumstances; must make all practical steps to help patient decide first (supported decision-making is a right); use least restrictive intervention; respect dignity, privacy, and autonomy; take account of known past/present wishes and views of interested (in patient's welfare) others (no hierarchy of relationships/authority given)

A patient's decision can be transmitted to the treating clinician in any manner that suits the patient (gestures, sign language, written, verbal, a third party)

If a person cannot be supported to make a decision the High Court or Circuit Courts appoints a personal guardian to act as substitute decision-maker re property/affairs

Certain decisions are reserved to the High Court, e.g. withdrawal of artificial life-support, non-therapeutic sterilisation, organ donation

Independent Office of Public Guardian supervises court-appointed guardians – if no one is able/willing to be a guardian the Office acts as guardian of last resort

The capacity required to make medical decisions depends on the decision to be made²⁵². The decision arrived at is less important than the rationality of the process whereby the individual arrives at the decision.

²⁴⁹ Of unsound mind and unable to handle his/her affairs.

²⁵⁰ 3rd Floor, 15/24 Phoenix Street North, Smithfield, Dublin 7. +353-(0)1-8886189 (tel), 8724063 (fax).

http://www.citizensinformation.ie/categories/justice/courts-system/office_of_wards_of_court/

²⁵¹ Gives effect to *Hague Convention on the International Protection of Adults* and *UN Convention on the Rights of Persons with Disabilities*.

²⁵² Roberts et al (2008, p. 1618-9) make the points that capacity, which must be subjected to a targeted assessment, cannot be assumed only from the diagnosis or from illness severity; capacity may change over time (e.g. mania settles) so that capacity may need to be reassessed; and that whilst a patient might display an understanding of facts he/she may not appreciate that they apply to him/her (e.g. 'I am divine and therefore it will not harm me/therefore I do not need the treatment.').

Should a patient defer completely to the physician's (or other's) judgement he/she should have his/her capacity to make such a waiver assessed and documented.

Testamentary capacity (capacity to make a Will at a particular point in time) is not usually questioned (i.e. they are admitted to probate and put into effect without court involvement), but may be (e.g. a child could apply to the court on the basis that the parent/testator failed in the moral duty to make proper provision for him/her). In reality, most bad decisions are made by people who are deemed competent! It is important for the assessor to record questions, answers and results of their examination in case of future legal involvement. (Posener & Jacoby, 2008) The doctor reporting on an examination for testamentary capacity should read as if addressed to the Court and not gloss over any deficiencies in his/her understanding of the case, e.g. if the testator's estate is unknown to the doctor except from the testator's own account then this fact should appear in the report.

Suffering from dementia does not *per se* invalidate a Will. The amnesic syndrome is very likely to interfere with one's ability to dictate a valid Will because of its effects on recollection and retention. Undue influence, which may be difficult to prove, might invalidate a Will.

The legal requirements for being of 'sound disposing mind' (make a valid Will) date to 1870 in the case of *Banks v Goodfellow*²⁵³ (see box). One can have the capacity to make a certain decision and yet, at the same time, not have capacity to make another decision as in the British *Park v Park* case of 1954 where a man validly married and invalidly made a Will within hours of one another!

A doctor may be asked retrospectively to assess if a person, perhaps deceased, had testamentary capacity at the time of making a Will. Such evidence may be as a witness of fact (the doctor was the testator's physician and is asked to deliver the facts he/or she observed personally) or as an expert witness .

Requirements for Will-making

Set out in Irish *Succession Act 1965*

There is no maximum age

Testator must

- **be at least 18 years of age or have been married**
- **be of 'sound disposing mind', even if this is only during a 'lucid interval'**²⁵⁴
- **must know that one will die and that the Will comes into operation after death, who the executor(s) is(are), that he/she can change the Will anytime before death, who will benefit what from the Will and who would expect to so benefit, what he owns²⁵⁵ (this need not be very exact), how a new will differs from a previous one, that some parts of property may not be given to certain people because others (say a spouse's rights to jointly owned family home²⁵⁶) have**

²⁵³ The delusions of John Banks did not interfere with his capacity to leave most of his estate to his niece.

²⁵⁴ A Will, once valid, will not become invalid just because the testator/testatrix later loses testamentary capacity as long as the person had such capacity when making the Will and retained this capacity until the Will was executed (drawn up and signed). When dealing with cases that might be contested (e.g. elderly or seriously ill) the solicitor should arrange for a medical examination and assessment of capacity: this is known in England as 'Templeman's golden rule' after the judge in *Re Simpson* of 1977 (see *Solicitors Journal*, 1977:121;224).

²⁵⁵ The solicitor's request to the doctor should state what is required and outline what the proposed testator owns and who might hope to benefit from the Will.

²⁵⁶ The Napoleonic Code (e.g. in France) restricts testamentary freedom by the idea of mandatory heirs.

rights in this area, and know why he/she is not leaving certain persons things in the Will

- **There must not be a delusion²⁵⁷ that *specifically* interferes with the terms of the Will (e.g. leaving the universe to his wife because of a grandiose delusion)**
- **Testator may not be able to speak or write but can indicate wishes to his/her executor (not to the beneficiary)**

The National Assistance Act 1948, section 47: A rarely used provision whereby a community physician may apply to a magistrate for an order to remove to hospital a vulnerable person who lives in a state of neglect or squalor.

'*The Bournemouth*²⁵⁸ gap': This referred to the absence of procedural safeguards in UK law for a patient who lacked capacity and where carers and professionals disagreed as to correct management. A similar dilemma exists in Ireland in the case of dementia sufferers who lack capacity who do not qualify (or cease to qualify) for involuntary admission under the *Mental Health Act, 2001* but who cannot be allowed to simply walk out of the hospital. Can they be placed in a nursing home without their consent (as often happens) or kept on as a 'voluntary' patient in a psychiatric facility (as sometimes happens)? Section 4 (best interests) of the *Act* only applies to involuntary patients.

A retrospective study of 115 consecutive psychiatric admissions of people who lacked capacity to make treatment decisions (Owen *et al.*, 2009c) found that 83% of those who regained capacity agreed retrospectively with the decisions made on their behalf.

Should patients be allowed to reject life-saving care? In 2009 the Law Reform Commission (LRC) recommended new legislation which would give patients the power to refuse life-saving treatment. The *advance care directives* (ACD, "living wills") would allow patients to make treatment decisions in advance, in case they suffer an illness or accident that leaves them unable to communicate their wishes directly. The LRC recommends that: an ACD would not change current legislation on euthanasia and assisted suicide; ACDs could include an instruction to refuse life-sustaining treatment but only if it is provided in writing and witnessed; ACDs would allow patients to refuse medical treatment on religious grounds; patients would not be able to refuse basic care (e.g. nutrition, hydration and hygiene); patients would be advised to seek medical advice when making an advance care directive (not mandatory); new legislation would not mean medical professionals would be legally liable if a directive they believe to be valid, later becomes the subject of an investigation; and professional bodies would be able to investigate medical practitioners who failed to honour an ACD. The LRC also believes a statutory code of practice on ACDs should be created to offer guidance for healthcare professionals.

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²⁵⁷ Some judges may decide that what psychiatrists term an overvalued idea amounts to 'a disorder of mind' (read 'delusion') despite the fact that such overvalued idea might be best understood to arise from the usual self (personality), as in *Dew v Clark & Clark* of 1926 in which a man had a persistent dislike of his daughter.

²⁵⁸ *R v Bournemouth Community and Mental Health NHS Trust Ex P.L.* (1998) All E.R. 289. An intellectually disabled man was taken into hospital informally (voluntary) against his carrier's wishes. The case eventually ended up in the European Court of Human Rights which ruled that the detention constituted deprivation of liberty under Article 5 of the *European Convention on Human Rights*. It would have been better to have used the mental health legislation if the patient had a mental illness and not to admit as a voluntary patient when the person lacks capacity.

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3

Forensic Psychiatry

4

Measures and scales in psychiatry²⁵⁹

Brian O'Shea

'A test is an objective measure in a sea of opinion, but its value depends on the discretion and understanding with which it is used.' (Freeman ea, 1992)

The *criterion instrument* ('gold standard') is one which we accept as being reliable and valid (see box). New measures are tested against the criterion instrument, e.g. the Hamilton Depression Scale. In practice, there is a trade-off between sensitivity and specificity (see box) when it is decided where at cut-off (threshold) lies (dividing 'cases' from 'non-cases').

Reliability²⁶⁰ is concerned with how well an instrument measures what it is being used to measure. It is a measure of the level of agreement between 2 sets of observations, agreement being usually measured by the correlation coefficient (good reliability if high and positive: +0.8 or more) which has a range of -1 to +1; *inter-observer* reliability is the extent to which different raters can agree when assessing the same group of patients with an instrument at the same time; *inter-rater reliability* describes assessments by different raters of the same material on two or more occasions; *split-half (split-instrument)* reliability refers to the division of items in a test into 2 halves – if all items measure same characteristic there should be a high correlation between both halves, a measure of *internal* reliability (similar to construct validity); *test-retest reliability* is tested when the test is given to a group on several occasions, allowing sufficient time to overcome memory artefact – useful for stable characteristics but may underestimate reliability for fluctuating variables; *alternative form reliability* describes 2 supposed similar forms of the measurement used to assess the same material simultaneously or immediately consecutively.

Inter-rater reliability tests include the kappa statistic²⁶¹ which assesses agreement between 2 observers and an outcome, and intraclass correlation²⁶² assesses agreement between observers when there are 3 or more observers and with interval data.

Validity: an instrument measures what the authors want it to measure, e.g. the Hamilton Depression Scale has validity because it measures depression and not personality factors; validity of psychiatric diagnoses is concerned with their meaningfulness and usefulness; *content*²⁶³ validity is the extent to which the items of a rating scale are representative of the disorder under investigation; *face* (basically the same as content validity) validity means that the instrument is congruent with clinical experience – it feels or looks right; *predictive* validity means an ability to foretell outcome or response to treatment; *construct* validity is the extent to which a scale's items can be added to give a total score without reduction of the information

²⁵⁹ Many measuring instruments used by psychologists and psychiatrists currently find greater research than clinical application. They should not be interpreted in isolation in individual cases, but rather they should be viewed within the context of the case as a whole, e.g. a very depressed individual will score badly on standard tests of intelligence. Before asking a psychologist to 'perform tests' it is wise to discuss the case with the psychologist, who will be able suggest the more appropriate battery of tests. The main applications of measuring instruments are case identification, standardisation of psychiatric interviews, and serial measurement of symptom severity. They can be helpful in standardising local, national and international reports.

Some important concepts are defined in one box (see, e.g. Tyrer ea. 1993) and a selection of instruments are described in another box.

²⁶⁰ Appropriate statistics for a continuous scale and a categorical measure are the intra-class correlation and Cohen's kappa respectively.

²⁶¹ Kappa ranges from -1 to +1 where -1 = no agreement (e.g. on diagnosis), 0 = agreement no better than chance, and +1 = complete agreement.

²⁶² Intraclass correlation gives estimate from -1 to +1 and the closer it is to +1 the more similar are the ratings for individual patients across observers, i.e. there is low variability.

²⁶³ The term '*descriptive validity*' means the extent to which various manifestations of a disorder/syndrome actually occur together in real life. This tendency to co-occur is measured with *latent class analysis*.

contained in the individual items²⁶⁴; *concurrent validity* describes a comparison of the measure being tested with an external valid yardstick concurrently (e.g. a new rating scale for depression with the HAM-D)²⁶⁵; *criterion validity* is the combination of concurrent and predictive validity; *incremental validity* tells us if the measurement is better than other measurements in approaching true validity; cross-validity describes validation of a measurement that has its criterion validity established for one sample and then is retested on another sample. *Ecological validity* refers to a growing awareness of the need to design tests the better predict real-life behaviour and functioning, e.g. many tests avoid fatiguing the patient or having much ambient noise whereas symptoms may be worst during the normal noise and bustle of a tiring day; an elderly man who performs poorly on mental arithmetic tests may still be able to manage his finances at home by using a pen and paper.

Sensitivity (true positive rate): proportion of true cases (identified using criterion instrument) identified as cases by a novel instrument.

Specificity (true negative rate): proportion of non-cases (identified using criterion instrument) identified as non-cases by a novel instrument.

Psychiatric rating scales can be divided into self-appraisal or self-rating on the one hand and observer-appraisal or observer-rated on the other. (Kugler, 1992) The orientation of rating scales for depression varies from a somatic bias (e.g. HAM-D) to a cognitive (e.g. BDI) bias. (Thompson, 1991) However, both the HAM-D and the BDI contain enough somatic complaints questions to give false positive depression scores. (Novy et al., 1995) Imprecision in psychiatric conceptualisation explains many problems in measurement. (Snaith, 1991)

Intelligence testing is expanded on further in one of the boxes. Projective testing, based on psychodynamic concepts and not used as much today as heretofore, are discussed in the chapter on personality and personality disorders. Personality tests tell us more about differences between groups of people and are relatively non-specific regarding individuals.

Various attempts have been made to measure individual subjective experiences and attitudes. Shapiro (1961) developed the *Personal Questionnaire* to measure symptom intensity and change over time from a patient's perspective. Osgood et al. (1957) advocated what they called the *Semantic Differential*, which measures psychological meaning of concepts. Kelly's (1963) *Role Construct Repertory Test*, and the associated *Repertory Grid Test*, aims to reveal a person's constructs or way of looking at the world. Constructs are presented as bipolar adjectives (big-small, friendly-hostile, etc) and cards are shown to the client naming people (called 'elements') with a significant role in his or her life. The chief use of such tests is in psychodynamic therapy, although they have wider applications.

Interviews

Clinical – conducted by a trained or trainee professional

Structured – (1) fully structured – questions and follow-up probes asked verbatim by trained, non-professional interviewers; and (2) semi-structured – questions asked verbatim by professional but considerable latitude is allowed to follow up on leads (individualised and contextualised approach)

Structured interviews have the advantages of improved reliability (reduced variability) and validity (diagnostic criteria are covered in a full and systematic way) and are useful in training (learning what questions to ask) and as research tools (cheap use of lay interviewers), but they may interfere with rapport, are subject to the validity of the classification system (e.g. DSM-IV-TR), may be poor at assessing severity²⁶⁶ (Jablensky, 2003, p. 206), and are a trade-off of breadth versus depth in that they don't cover all disorders/topics. (Segal & Coolidge, 2007)

²⁶⁴ Extent to which parts address a common construct. For a scale we measure with Cronbach's coefficient alpha (varies 0 to 1; 0.6-0.8 = moderate internal consistency; >0.8 = high internal consistency).

²⁶⁵ If there is no known gold standard for comparison one tests for *known group validity*, i.e. can a measure distinguish members of two groups.

²⁶⁶ Concerns that lay interviewers conducting structured diagnostic interviews have been raised, one criticism being that they inaccurately assess severity of symptoms. (Jablensky, 2003, p. 206) However, Segal and Coolidge (2007, p. 83) believe that structured interviews allow determination of severity and impairment because they incorporate systematic ratings.

Unpublished scales should be viewed with suspicion. For example, Marshall ea (2000) argue that their use in treatment trials in schizophrenia may bias the results in favour of the treatment of interest over the control intervention.

Definitions

Proband (propositus): index case – the original individual under consideration in relation to a stated characteristic, such as his disease.

Morbid risk: lifetime expectancy or lifetime incidence of a disorder – proportion of people who would develop a disorder if followed through entire period of risk; one way of expressing rate of an illness; in order to allow for high risk ages it may be necessary to correct for actual age. Perälä ea (2007: DSM-IV, Finland) estimated the lifetime prevalence of all psychotic disorders to be 3.06% (using register data this rose to 3.48%) and for schizophrenia, 0.87%; schizoaffective disorder, 0.32%; schizophreniform disorder, 0.07%; delusional disorder, 0.18%; bipolar I disorder, 0.24%; psychotic major depression, 0.35%; substance-induced psychosis, 0.42%; and psychosis secondary to a general medical condition, 0.21%.

Stability: the variability of scores when a test is repeated on the same individual; little variation indicates high reliability; tests may possess equivalent forms to counter memorisation in test-retest situations (see split-half reliability).

Standardisation: availability of normative data, such as IQ scores in a suitable population, for the index test, such as IQ, to allow comparison with future test results.

Bottom drawer phenomenon: negative findings less likely to be published, which may bias literature toward positive results. See Cuijpers ea (2010) for publication bias in research on CBT and adult depression.

Response set: a source of error resulting from excessive responses to propositions.

Bias towards the middle: a responder's tendency to rate his responses in a way that avoids excesses.

Hawthorne effect: tendency for patients to fare better in research study than in clinical practice; may be related to selection criteria or increased personal attention. The term was coined in 1955 by Henry A Landsberger who examining earlier research work performed at the Hawthorne (electricity) Works near Chicago: almost any intervention increased workers' productivity by virtue of the attention offered by researchers.

Halo effect: the observer tends to answer in a way that conforms with his initial impressions; if a student has handed up a poorly written exam paper the assessor may fail to detect any good in its content.

Proximity: if two items are placed closely together in a scale the rating given to one may psychologically affect the rating given to the one beside it.

Defensiveness: answers are given in such a way that certain information is not revealed.

Von Domarus error: considering 2 different things as equal because of a single shared property.

Effort after meaning: people with a disorder remember events imagined to be causative rather than giving an objective account of all pertinent details.

*Yerkes-Dodson Law*²⁶⁷: performance increases gradually with increasing arousal until peak performance is reached; as arousal increases further performance declines.

Social desirability: a further cause of error, leading to a reduction in accuracy at the expense of what is deemed to be acceptable.

Reactivity: degree to which behaviour changes as a result of being assessed; potential problem for naturalistic observation studies and self-recording techniques; difficult to overcome, even with unobtrusive measures.

Carry-over effect: drug continues to exert some effect after administration is discontinued; may contaminate results in a crossover trial.

Selected individual instruments, alphabetically listed

Beck Depression Inventory (BDI-II): from A Beck and colleagues; patient (13 years of age or older) chooses one of a number of severity statements from symptom and attitude categories that come nearest to recent experience; does not say why patient is depressed. Both BDI and GHQ were developed as symptom inventories and not as diagnostic instruments. (Ennis ea, 1989) BDI and other self-report depression inventories can give misleadingly high picture of

²⁶⁷ This Law was published in 1908. During WWI, the American psychologist Robert Mearns Yerkes (1876-1956) and John D Dodson devised scales to measure IQ in order to weed out unsuitable recruits and to find suitable 'officer material'.

prevalence of depressive illness in distressed populations (e.g. self-harm admissions or those with chronic pain²⁶⁸) and include many with personality disorders. It has been suggested that the BDI could simply be replaced by an acknowledgement that 'my future seems dark to me'!

Brief Psychiatric Rating Scale (BPRS): short instrument devised by Overall and Gorham in the '60s; 18 symptom constructs, each rated on a 7-point severity scale; presents difficulties in sorting out different 'neurotic' disorders; mainly for psychiatric inpatients, especially psychoses and long-stay, i.e. severe illness; useful when determining effects of drugs on symptoms; symptom profile and a computer used to render a diagnosis.(see Leucht ea, 2005)

Cambridge Mental Disorders of the Elderly Examination (CAMDEX; Roth ea, 1986): standardised instrument for diagnosis of mental disorder in elderly, especially early detection of dementia. Three main sections: structured clinical interview with patient; range of objective cognitive tests; and structured interview with informant. Acceptable to patients; has a high inter-rater reliability; and cognitive section has high sensitivity and specificity. CAMCOG is the computerised version of the CAMDEX.

Clinical Interview Schedule (CIS; Goldberg ea, 1970): partially structured psychiatric interview for community survey work on minor psychiatric problems and requiring training before use.

Combat Exposure Scale (Keane ea, 1989a): subjective, quantitative assessment of wartime stressors, from light (1) to heavy (5) exposure.

Composite International Diagnostic Interview²⁶⁹ (CIDI; Robins ea, 1989) is a standardised interview that can be used by trained lay people or by the patient. Questions have to be asked in a defined way. A computer gives ICD or DSM diagnoses. It may have exaggerated prevalence rates for some disorders.

Eating Attitudes Test (EAT; Garner & Garfinkel, 1979): shortened, 26-item version in use; evaluates behaviours and attitudes found in anorexia nervosa (AN); cut-off point is used to distinguish AN from normal controls; has its limitations because classic eating disorders are uncommon which is said to greatly reduce its positive predictive value, i.e. the proportion of true cases divided by the number scoring positive on the test.(Williams ea, 1982) Using the EAT, Halpin & Fitzgerald (1992) found that 2.8% of Dublin adolescent males scored above the cut-off point, whereas between 6.8% of London schoolgirls score positively and 13% of Dublin schoolgirls score highly.

Edinburgh Postnatal Depression Scale (EPDS; Cox ea, 1987): not for use with 'blues', puerperal psychosis, anxiety disorder, phobias or personality disorder. Useful in primary care. Ten self-report statements looking at how woman felt in the past 7 days, not just today. While it has a cut-off point, the authors suggest an accompanying clinical assessment. Can be repeated after 2 weeks in borderline cases. Underline answer that is closest to how she feels, e.g. 'I have felt sad or miserable': Yes, most of the time; Yes, quite often; Only occasionally; No, never.

General Health Questionnaire (GHQ; Goldberg, 1972): long (60 items) and short (30, 28, 20 and 12 items) versions; self-administered; looks for recent changes, i.e. symptoms; a screening test for non-psychotic illness to be used in community, primary care,(Crossley ea, 1992) or general medical outpatient setting; does not give a diagnosis. In one 3-city British study,(Platt ea, 1991) housing conditions most powerfully predicted GHQ caseness – psychological disturbance was associated with a woman having inadequate housing, having a low income or being personally unemployed, having no co-resident with a job, and bringing up children without a partner's support. A scaled version exists with symptom subscales for somatic symptoms, anxiety and insomnia, depression, and social dysfunction.(Goldberg & Hillier, 1979)

Geriatric Depression Scale (GDS; Brink ea, 1982; Brink, 1984; Yesavage ea, 1983): self-rating; can be read to elderly or answered in writing; minimises purely somatic symptoms (very common in this age group, e.g. constipation) emphasised in the Zung and Hamilton scales; not accurate in the presence of significant dementia; simple yes/no answers; 30 questions; 1 point for each depressive answer; final score: 0-10 normal; 11-20 mildly depressed; 21-30 moderate to severe depression. There are also shorter versions of the GDS: 4, 5, 10, and 12-item versions.

Geriatric Mental State Schedule (GMSS; Copeland ea, 1976): a research instrument taking three quarters of an hour to administer; used to assess psychopathology; AGE-CAT, a computerised algorithm, provides diagnoses.

Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974): assesses initial severity of the event (head injury); measures 3 clinical features, i.e. eye movement (from spontaneous eye opening to never opening), best motor responses (from obeys command via decerebrate state to no response), best verbal response (from orientated to silence); coma is present with a score of less than 8. Minimum score = 3, maximum score = 15 (there is no zero score):-

Eye opening: spontaneous (4), to speech (3), to pain (2), none (1).

Best motor response: obeys commands (6), moves within general locality (5), withdraws (4), abnormal bending & flexing of muscles (3), involuntary straightening and extending of muscles (2), none (1).

Verbal response: orientated (5), confused in conversation (4), use of inappropriate words (3), incomprehensible (2), none (1).

A paralysed and intubated ICU patient can score 3 despite full consciousness!

²⁶⁸ Longson (2007, p. 97) criticised the BDI because inclusion of somatic symptoms over diagnoses depression in physically ill patients.

²⁶⁹ Developed from Robins' earlier *Diagnostic Interview Schedule (DIS)*.

Hachinski ischaemic score (HIC: Hachinski, ea, 1975): the higher the score the more likely dementia is due to cerebrovascular disease: abrupt onset (score 2), stepwise deterioration (1), fluctuating course (2), nocturnal confusion (1), relative preservation of personality (1), depression (1), somatic complaints (1), emotional incontinence (1), history of hypertension (1) or strokes (2), evidence of associated atherosclerosis (1), focal neurological symptoms (2) or signs (2) - not very accurate but helpful - score < 4: probable Alzheimer's disease; 4-7: probable mixed Alzheimer's and multi-infarct dementia (MID); > 7: probable MID. The HIC was derived from patients who were relatively young and mildly impaired.

Hamilton Rating Scale (HRS) for Depression (HAM-D or HRSD or HDRS; Hamilton, 1960): standard for other scales (e.g. Carroll's); measures depression but does not diagnose it; used in drug trials; useful during ordinary interviews; not a good test to repeat on the same individual; more sensitive to physical than existential symptoms; may not distinguish clearly between symptom frequency and intensity. (Kugler, 1992) Has a number of items such as anxiety, psychic and somatic (nos. 10, 11), and insomnia (4,5,6) that respond to sedation. (see O'Shea, 1989)

Hamilton Anxiety Scale: same author (Max Hamilton) as HAM-D; picks up both somatic and psychic components of anxiety; includes some depressive symptoms; measures severity of anxiety syndrome rather than of the symptom of anxiety. (contrast with CAS above)

Hopkins Symptom Checklist (HSCL; Derogatis ea, 1974) self-report inventory of current psychiatric symptoms, e.g. somatisation, obsessive-compulsive behaviour, interpersonal sensitivity, depression and anxiety. *Inpatient*

Hopelessness Scale (HS; Beck ea, 1974): self-rating scale; 20 statements of thoughts or feelings about the future that subject rates as true/false. Hopelessness found to be a better discriminator than depression (on BDI) in distinguishing between unemployed, who had scored high on HS, and employed male parasuicides in Edinburgh. (Platt and Dyer, 1987) Aish and Wasserman (2001) wondered if the whole could be replaced simply with 'my future seems dark to me'!

Hospital Anxiety and Depression Scale (HAD; Zigmond & Snaith, 1983): used to detect states of anxiety (A) and depression (D) in hospital medical out-patient departments and in primary care; brief; limited to the 2 most common aspects of mood disorder presenting in hospital practice; has 14 items, 7 for anxiety and 7 for depression. Items representing symptoms of severe mood disorder (e.g. suicidal feelings) or bodily symptoms likely to be found in physical illness have been excluded. Scores of 11 or over on either scale suggest the presence of the relevant disorder and a total score of at least 18 means that the patient is likely to be distressed. Reliably used in primary care settings, e.g. in its Arabic version, (EL-Rufaie & Absood, 1987) and in non-psychiatric inpatient units. (Abiodun, 1994) Barczak ea (1988) used it and found a 31% prevalence of DSM-III psychiatric disorder in a genito-urinary clinic population. Chaturvedi (1991) found total HAD scores to be more clinically meaningful than subscale (A and D) scores.

Mini-Mental State Examination: quantitative test of cognitive functioning. This is covered elsewhere.

Minnesota Multiphasic Personality Inventory²⁷⁰ (MMPI; Hathaway & McKinley, 1943): contained 550 statements grouped into 9 scales (e.g. 'paranoid' scale); results plotted to produce personality profile; not to be used for normal personalities; validated on psychiatric patients; contains a 'lie' scale (assessment of test-taking attitudes)²⁷¹. The current scale (MMPI-2, 1989) contains 567 items with a forced choice yes/no format. The relevance of the MMPI to current psychiatric disorders is complicated by differing underlying theoretical constructs, and the profile may not tally with clinical insights. (Yates ea, 1998) A high score on a given scale does not necessarily mean that the respondent has that psychiatric disorder. (Kaslow & Farber, 1998) The *MMPI-A* is for adolescents (13 years of age onwards) and includes items relating to matters such as family and school difficulties and obsessiveness.

Montgomery-Asberg Depression Rating Scale (MADRS; based on 10 items of the *Comprehensive*

Psychopathological Rating Scale (CPRS) of Asberg ea (1978) - sadness, inner tension, inability to feel, pessimistic thoughts, lassitude, concentration difficulties, reduced appetite, reduced sleep, suicidal thoughts, and apparent sadness on observation - measures psychic but not somatic symptoms; may be more sensitive than HAM-D. (Montgomery & Asberg, 1979).

National Adult Reading Test (NART; Nelson, 1982): a reliable measure of premorbid IQ and educational level, including among patients with schizophrenia; (Crawford ea, 1992; Morrison ea, 2000) 50 short, irregular words to be pronounced, such as 'gauche', i.e. words that do not follow normal pronunciation rules; depends more on prior knowledge of pronunciation²⁷² than current cognitive capacity. An alternative to the NART is the *Wechsler Test of Adult Reading* (WTAR). (The Psychological Corporation, 2001) Both these tests have ceiling effects. The effects of culture and education must be taken into account. Dyslexia may reduce the usefulness of NART and WTAR results.

Neuroticism, Extroversion, and Openness Personality Inventory (NEO-PI; Wiggins & Pincus, 1992) measures 5 central facets of personality. The revised version (NEO-PI-R; Costa & McCrae, 1992) measures the following 5 facets

²⁷⁰ J Chamley McKinley, a psychiatrist, and Starke R Hathaway, a psychologist, compared the responses of patients with those of visitors to university hospitals in Minneapolis. Many years passed before the test was accepted for publication.

²⁷¹ Extremely high scores on this scale were obtained by the present author in Munchausen patients. The **MMPI validity scales** are the **L** (Lie - unsophisticated attempt to deny problems), **F** (Infrequency - excess endorsement of uncommon symptoms in order to appear ill), **K** (Correction - subtle attempts to deny problems), **VRIN** (Variable response inventory - inconsistent answering of similar items), **TRIN** (True response inventory - answering contradictory items as if they were similar), and **F_B** (F back - to test for inaccurate responding as the patient reaches the later items in the MMPI) scales.

²⁷² Relatively resistant to intellectual decline.

of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness; each facet includes 6 subscales, e.g. 'neuroticism' includes anxiety, anger/hostility, depression, self-consciousness, impulsiveness, and vulnerability.

Nurses' Observation Scale for In-patient Evaluation (NOSIE; Honigfeld & Klett, 1965): originally consisted of 80 items of ward behaviour completed by a pair of nurses using a 0-4 frequency of occurrence format for each item; later refined to a 30 item (NOSIE-30) scale; sensitive to effects of treatment over time; economical and accurate means of systematically assessing patient status and change (Honigfeld, ea, 1966); used with chronic schizophrenia patients.

Present State Examination²⁷³ (PSE): covers symptoms of previous 4 weeks; use probe questions before asking for details; 140 items; groups of items are rated to produce 'syndromes', e.g. situational anxiety; latter are then processed by a computer programme, *CATEGO*, to yield a standard diagnosis; psychiatrists need training before using PSE; poor for some areas, especially organic disorders, alcoholism, personality disorder, and intellectual disability; less reliable for anxiety than for depression; used in international comparisons and in local research, including medication effects in schizophrenia; high inter-rater reliability, with the exception of assessments of behaviour. A screening version is available. The *PSE Index of Definition* (ID; Wing ea, 1978) uses data from either the full or a 40-item version (there is also a 10-item version) of the PSE to give a score of 1 to 8 on the likelihood of having a psychiatric illness, when 5 or more means a 'probable' case; used to identify 'caseness' (having a disorder) in epidemiology. Expanded version of PSE (*SCAN*) covers episode-specific (current or representative) as well as lifetime diagnosis²⁷⁴.

Scale for Assessment of Negative Symptoms (SANS) and Scale for Assessment of Positive Symptoms (SAPS). Developed by Nancy C Andreasen, Iowa. SANS: comprehensive assessment of negative symptoms in schizophrenia (Andreasen, 1982, 1983, 1989); 5 scales evaluating 5 different aspect of negative symptoms: alogia, affective flattening, avolition - apathy, anhedonia-asociality, and attentional impairment; each symptom can be rated globally; also, detailed observations are made to achieve global rating. SAPS: complements SANS (Andreasen, 1984); allows detailed evaluation and global ratings of hallucinations, delusions, positive formal thought disorder, and bizarre behaviour. SANS and SAPS together provide comprehensive set of rating scales measuring schizophrenic symptoms and assesses change over time. Affective flattening includes unchanging facial expression, decreased spontaneous movements, paucity of expressive gestures, poor eye contact, affective non-responsivity, lack of vocal inflections, and a global score. Alogia includes poverty of speech, poverty of content of speech, blocking, increased latency of response, and a global score. Avolition - apathy involves grooming and hygiene, impersistence at work on school, physical anergia, and a global rating. Anhedonia-Asociality includes recreational interests and activities, sexual interest and activity, ability to feel intimacy and closeness, relationships with friends and peers, and a global score. Attention, apart from a global rating, involves social inattentiveness and inattentiveness during mental status testing. Peralta ea (1992) performed a factor analysis using both the SANS and SAPS and were unable to divide up schizophrenia in this way: the positive-negative dichotomy appeared to be an oversimplification, and the SAPS have low internal consistency.

Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978): structured interview using Research Diagnostic Criteria (RDC); symptoms assessed on 7-point scale; score of 3 or more is clinically significant; each symptom and rating criterion is defined; each symptom separately assessed for maximum severity for current episode and for past week; also assesses past episodes; chiefly for inpatients; not useful for organic disorders or anorexia nervosa, but purports to be useful in making most diagnoses using RDC; 3 versions are SADS, SADS-L or lifetime version which might be used for someone currently well, and SADS-C or change version that can be used for looking at changes in clinical state.

Suicide Intent Scales: Beck ea (1974) used such a scale in the early '70s that consisted of a series of scored questions dealing with circumstances surrounding a suicidal act and self-report of mental state at the time of the act. By adding 2 items dealing with the medical risk of the act and by changing some other components, an Intent Score (IS) Scale was formed. Circumstances score was high in men, older patients and physically ill patients, while self-report scores were high in patients with a past history of psychiatric therapy or previous attempted suicide. Pierce (1981) found that, in a 5-year follow-up, future suicides tended to have high scores on a scale for their original self-injury episodes and had very high scores for the penultimate self-injury before suicide. The fact that suicides had made an average of nearly 3 non-fatal attempts emphasises the importance of repetition along with high intent in predicting at least some suicides. Harriss ea (2005) found that suicide intent scores appeared to have most value in assessing short-term suicide risk.

Tower of London Test²⁷⁵: the test involves moving coloured beads on three upright poles in order to produce a pattern determined by the examiner; the subject must be able to plan moves (break down the task into parts and follow a sequence of moves); worst results are found with left frontal lobe damage; not surprisingly, patients with schizophrenia also perform poorly here.

²⁷³ Associated with John Wing.

²⁷⁴ **Schedule for Clinical Assessment in Neuropsychiatry (SCAN;** Wing ea, 1990) is a semi-structured interview employed by professionals and used with adults. Included are PSE-10, a glossary of symptom definitions, direct rating of symptoms with Item Group Checklist, and ICD-10 and DSM-IV diagnoses via Clinical History Schedule. The diagnosis is made by a computer.

²⁷⁵ This was derived from a puzzle known as the Tower of Hanoi.

Wechsler Adult Intelligence Scale (WAIS-III, ages 16-84): most commonly used IQ²⁷⁶ test (Wechsler, 1997); useful in confirming clinical impression of organic mental deterioration - latter depends on fact that verbal abilities are more resistant to impairment than performance; if there is more than 20-point difference between performance and verbal scores organic impairment is likely (a lesser discrepancy should be treated with caution: Rao & Swanson, 2003, p. 31); WAIS has 12 subtests (6 measure verbal ability [information²⁷⁷, comprehension²⁷⁸, arithmetic²⁷⁹, similarities²⁸⁰, digit span²⁸¹, vocabulary²⁸² - a seventh, optional subtest is called letter-number sequencing²⁸³] and 6 are performance tests [digit symbol²⁸⁴, picture completion²⁸⁵, block design²⁸⁶, picture arrangement²⁸⁷, matrix reasoning²⁸⁸, symbol search²⁸⁹]); standardisation for age and further calculation yield verbal, performance, and full-scale IQs²⁹⁰. Selective impairment of cognitive function may lead to abnormal scattering of scores on the WAIS. In organic cerebral disease those tests reliant on memorisation of recent events and on perceptual motor control will exhibit greater deterioration in scores than tests that depend on vocabulary and general knowledge. Grey areas in clinical certainty usually correspond with shortcomings in psychological reporting. No instrument supplants a comprehensive mental state examination²⁹¹. The *Wechsler Abbreviated Scale of Intelligence (WASI)* was introduced in 1999. The **Wechsler Memory Scale-III (WMS-III)**²⁹² gives a memory quotient (MQ) that allows for age - various aspects of memory are tested, e.g. recall of stories related by the examiner²⁹³; in brain trauma IQ and MQ correspond fairly closely to each other; in dementia the MQ will score inferior to the IQ; when the WAIS Verbal IQ score is greater than the Performance IQ score a lesion of the right side of the cerebrum is probable but it could be bilateral; the opposite situation favours a left-sided lesion. The dominant hemisphere is the left hemisphere in most people, including left-handed (sinistral = left-handed, dextral = right-handed). The *Bender-Gestalt Test for Geometric Designs* and the *Graham-Kendall Memory for Designs* are other useful procedures; the latter, as with the Bender, measures visuo-motor control and it also examines immediate visual memory. The *Halstead Category Test* that addresses conceptual thinking detects damage to the frontal lobes. The *Rey-Osterreth Test* looks for dysfunction of the dominant frontal and temporal areas. The **Wisconsin Card Sorting Test (WCST; Berg, 1948)** also detects frontal lobe damage. In the WCST, the participant has to sort cards into 4 heaps according to a sorting rule deduced from feedback supplied after each trial; once the rule is deduced, it is changed arbitrarily without any warning and the new sorting rule has to be deduced. Feinberg (1997) disagrees with using the WCST in patients with schizophrenia saying that they score badly because of poor motivation and attention and difficulties with trusting others. Indeed, a meta-analysis²⁹⁴ (Laws, 1999) suggests that really what is being picked up is only part of a general intellectual dysfunction. The *Token Test* is used to detect receptive language disturbance. Parallel versions of tests may allow serial testing, e.g. the use of the Benton Visual Retention Test (patient studies and tries to reproduce 10 designs) to investigate perceptual function. Batteries of tests are useful when assessing dementia, e.g. the *Kendrick Battery* and the *Clifton Assessment Procedures for the Elderly (CAPE)*. *Raven's Progressive Matrices*, an assessment of non-verbal visuospatial abilities, attempts to tap 'observation and clear thinking' and employs a set of matrix tests of different age groups, including adults; you are asked to select a pattern piece that is missing from the matrix; the raw score is expanded as a percentile; even poorly educated people can score well; correlates fairly well with IQ scores; may be superior to WAIS for very high intelligence levels. The *Mill Hill Vocabulary Scale*, an

²⁷⁶ Gale ea (2007) suggest that bright children often turn out to be adult vegetarians!

²⁷⁷ Wide variety of information in order of difficulty (N = 19).

²⁷⁸ Meaning of proverbs, next step in defined circumstances, etc (N = 16).

²⁷⁹ Arithmetical problems set in everyday activities (N = 14). *The only timed verbal subtest.*

²⁸⁰ In what way are 2 things alike (N = 14)?

²⁸¹ 3-9 digits repeated forwards and 2-8 backwards. This is a good test of working memory.

²⁸² Patient must give meaning of 35 words of different degrees of difficulty.

²⁸³ The patient must extract separate sequences of letters and numbers from a mixture of both.

²⁸⁴ Quickly follow a code in order to match symbols and digits.

²⁸⁵ Quickly follow a code in order to match symbols and digits.

²⁸⁵ Timed test: 20 pictures (e.g. faces) are presented with a missing part, but which part is missing?

²⁸⁶ Timed test: The patient must reproduce designs using red and white blocks.

²⁸⁷ Cartoon pictures (10 sets) must be arranged sensibly into a story.

²⁸⁸ This is thought of as a non-verbal measure of ('fluid') IQ. Patient must choose the next in a sequence of abstract coloured symbols. This is derived from *Raven's Progressive Matrices (Q.V.)* and replaces 'object assembly' subtest of WAIS-R. *The only non-timed performance subtest.*

²⁸⁹ The patient looks for either of 2 symbols in a sequence.

²⁹⁰ All 3 IQ scores have a mean of 100 and SD (standard deviation) of 15: a difference of 15 points between verbal and performance IQs is statistically significant and carries clinical implications. Each of the WAIS subtests have a mean score of 10 and an SD of 3.

²⁹¹ Some brain-injured subjects can score within the normal range on the WAIS despite being unable to work because of (frontal) apathy, memory problems and are slow at processing information. (Carson ea, 2007, p. 337) An attempt to correlate cognitive tests with white matter lesion density in the elderly revealed that the association was significantly influenced by IQ at age 11. Therefore, what appears to be due to change due to age may actually stem from inherent ability. (Deary ea, 2006)

²⁹² The WMS-IV is being developed currently.

²⁹³ Information, logical memory, faces, verbal paired associates, letter-number sequencing, and spatial span are non-optional components in WMS-III, whereas word lists, visual reproduction, mental control, and digit span are optional.

²⁹⁴ Looking at WCST and, as an index of general intellect, the WAIS.

intelligence test, measures verbal ability. Useful sources of information on this subject are Mittler(1973) and Lishman(1978).

Wechsler Intelligence Scale for Children (WISC-IV): for children aged 7-16 years; verbal and non-verbal abilities tested; the WISC-R-UK and WISC-R-S versions use norms from UK and Scotland respectively.

Wechsler Preschool and Primary Scale of Intelligence (WPPSI): for children aged 3-7 years; the WPPSI-R-UK uses UK norms.

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman ea, 1989): specific measure of symptom severity in OCD (during preceding week) uninfluenced by type of obsession or compulsion; 10-item, 40-point semistructured instrument, each item rated by clinician from 0 (no symptom) to 4 (extreme symptom), with a total range of 0-40; separate totals for obsessions and compulsions. A childhood version is available.

Zung Self-Rating Depression Scale: devised by W Zung, 1960s; patient asked to quantitate 20 sentences; poorly correlated with observer ratings; insensitive to change with treatment; fallen into disfavour.(Lee, 1998) The *Zung Observer-Rated Depression Status Inventory* followed nine years later.

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5

Electroencephalogram, neuroimaging²⁹⁵ and sleep Brian O'Shea

'...the hallucination/Broca's area claim is trapped in an unresolvable ambiguity for there is no way of telling whether the subject reports an auditory image or the belief that he is having one'. (Berrios & Marková, 2002)
'The neuroanatomical maps ...used to localize activation may not be identical throughout the literature. Despite anatomical proximity, these areas may have very different connectivity patterns'. (Ebmeier & Kronhaus, 2002)

According to Freud, dreaming employs primary process thinking and may represent discharge instinctual drives repressed by day. The 'non-dreaming' part of the sleep cycle²⁹⁶ may be involved in body tissue restoration. Sleep seems important for memory consolidation and immunity. The dreaming component may entail brain tissue restoration, non-specific casting off of excess neuronal load, or intrusion of events from the previous day (*day residue*) to influence dream content. Young obese people were found to have relatively little REM sleep in one study. (Liu et al, 2008)

Pooled data on over 1.3 million subjects around the world (Cappuccio et al, 2010) suggests that sleeping less than 6 hours/night is associated with a 12% increased chance of premature death compared to sleeping 6 to 8 hours. Excess sleep (> 8 hours/night) is associated with a 30% greater risk of death.

The ascending reticular activating system (RAS²⁹⁷), extending upwards from medulla to thalamus, exerts tonic control on arousal and consciousness.

Brain components of arousal vs sleep promotion

Arousal

Ascending RAS – main arousing system: two main branches are:

1. Thalamo-cortical arousal branch – contains cholinergic neurones from laterodorsal tegmental pedunculo-pontine tegmental nuclei → thalamus → cortex
2. Hypothalamic-aminergic arousal branch – serotonergic (dorsal raphe), noradrenergic (locus coeruleus) and histaminic (tubero-mammillary) → lateral hypothalamus → basal forebrain

Sleep promotion

Ventrolateral preoptic area (VLPO – 'sleep centre') of anterior hypothalamus – inhibits both branches of ascending RAS – GABA and galanin are main neurotransmitters

REM-non-REM sleep switching

REM-active neurones of extended VLPO

Wake-sleep switching

Lateral hypothalamus peptides orexins A & B (aka hypocretins 1 & 2)

Tubero-mammillary nuclei

VLPO

Suprachiasmatic nucleus²⁹⁸

²⁹⁵ Walter Edward Dandy (1886-1946), neurosurgeon at Johns Hopkins, described the injection of air (as contrast medium) into peri-spinal space (and thence into the ventricles: air encephalography/ventriculography) in 1918/19.

²⁹⁶ Dreams do occur in this phase, albeit with poorly formed, non-narrative imagery.

²⁹⁷ The RAS includes the brainstem reticular formation (ventral medulla, central pons, and midbrain), posterior hypothalamus, subthalamus, nucleus basalis of Meynert, septal nuclei, diagonal band, and certain thalamic nuclei (ventromedial, intralaminar, and midline). There are two RAS pathways: dorsal (forebrain to thalamus to forebrain cortex) and extra-thalamic (subthalamus, posterior hypothalamus and basal forebrain project straight to whole of cortex).

²⁹⁸ The SCN can function autonomously (without external zeitgebers – free running state) but it can be entrained by zeitgebers (entrained state).

Flip-flop switch for REM sleep²⁹⁹ – suggested in rodents (Lu et al., 2006)

Stimulation of the RAS causes EEG desynchronisation and behavioural arousal. Lesioning of the RAS leads to permanent sleep, although destruction of parts of it, such as the median raphe, causes permanent insomnia. Basal forebrain cholinergic magnocellular neurones project throughout the cortex and appear to play an important part in the maintenance of cortical arousal.

Sleep and chronobiology³⁰⁰

There are two main theories of sleep³⁰¹ energy conservation and energy restoration. As sleep progresses the episodes of non-REM (or n-REM) sleep shorten while those of REM lengthen. The metabolic rate decreases at night, and especially during sleep, by 5-25%. Animals seldom attacked, such as horses, sleep much longer than those in constant danger, like bats. When much growth is required³⁰² slow wave sleep and the overall amount of sleep are increased. When less sleep is needed, as in hypothyroidism, the amount of slow wave sleep is diminished. ATP (adenosine triphosphate) derived from cells is consumed during periods of protein degradation; cell mitosis increases during sleep and ATP concentrations increase in association with protein synthesis.

Deficiency of melatonin³⁰³, which is produced from serotonin by the pineal gland at night and has a role in sleep-wake cycle regulation, or disruption of its rhythms has been suggested as explaining the increased prevalence of sleep disorders with advancing age. Melatonin does not induce sleep in nocturnal rodents. During winter, melatonin indirectly affects the gonads to reduce reproduction potential, a fact that is of particular relevance in season-breeding reptiles, amphibians, and birds. (Tamarkin et al., 1985) Haimov et al. (1994) hypothesise that a lack of exposure to bright light in institutions may deplete 6-sulphatoxymelatonin (6-SMT, major urinary measure of melatonin) excretion in old age. Garfinkel et al. (1995), looking at elderly insomniacs, found reduced or delayed peak nocturnal 6-SMT excretion; 2 mgs. controlled-release melatonin corrected the insomnia. According to Famuyiwa and Adewuya (2008) the effectiveness of melatonin in getting children with neurodevelopmental disorders to sleep is questionable and it has a potential for causing adverse effects; sleep hygiene measures should take precedence in such cases. Anonymous (2009) states that the evidence for the use of melatonin for primary insomnia is limited. Melatonin may stabilise sleep onset time in some blind subjects. (Arendt et al., 1995) In sighted humans melatonin is excreted early in the sleep cycle whereas blind people³⁰⁴ have irregular 24-hour rhythm and

²⁹⁹ The putative *flip-flop switch* consists of mutually inhibitory REM-off and REM-on GABA-ergic mesopontine tegmental areas. The REM-on area has two groups of glutamatergic neurones – one projects to basal forebrain to regulate EEG in REM and the other travels to medulla and spinal cord to regulate REM atonia.

³⁰⁰ Foster and Kreitzman (2004) and Mendlewicz (2008) provide readable introductions to this topic. See also complete issue of *Dialogues in Clinical Neuroscience* 2007; 9(3).

³⁰¹ Which fail to comprehensively explain all that is known about sleep. The *homeostatic model* emphasises need for sleep (stronger with time awake – adenosine, an inhibitory neurotransmitter, plays a role here) while the *circadian model* states that sleep propensity has a circadian (24 hour) pattern for sleepiness and attention. Depending on clock time, circadian issues can attenuate or promote homeostatic drive.

³⁰² Pregnancy, exercise, sleep loss, hyperthyroidism, adolescence, refeeding in anorexia nervosa, etc.

³⁰³ 5-O-methyl-N-acetylserotonin. Drugs capable of changing the *circadian clock*, such as in rodents, are known as chronobiotics. The suprachiasmatic nucleus (SCN) contains highly expressed melatonergic receptors. There seems to be a two-way feedback between melatonin and the SCN. Synthesis and timing of melatonin production depends on afferent signals from the SCN; the SCN projects to the pineal gland via the paraventricular nucleus and the latter projects to the spinal cord; ascending cord fibres synapse in the superior cervical ganglion which projects in turn to the pineal gland (such connections are disrupted in *tetraplegia* [upper cord lesion] and thus rhythmic melatonin production is not possible). Daily injections of melatonin can entrain the activity cycle of rodents kept in perpetual darkness. The antidepressant agomelatine is agonist at melatonin MT1 and MT2 receptors and antagonist at 5-HT_{2C} receptors. Given to depressed patients, agomelatine restores sleep pattern by redistributing slow wave sleep in the first nocturnal cycles but it does not suppress REM sleep.

Fruit flies were important in discovering how circadian clocks (transcriptional regulatory loop wherein each calculates its 24-hour period via an oscillating cycle of transcription and translation), with a similar mechanism throughout much of biology, work. *Drosophila* containing long- and short-day and arrhythmic mutants was to lead to similar discoveries in other living creatures. A majority of the various implicated genes (e.g. *period*) are found in flies and *Homo sapiens*.

³⁰⁴ Hypernyctohemeral (or non-24-hour-day or free-running) **syndrome resembles normals in time-free environment (non-24 hour circadian rhythm that is not entrained to astronomical time) and occurs in blind people or socially isolated (a similar problem is reported in schizophrenia); sleep-wake cycle delayed by 45 minutes later each day;**

melatonin excretion patterns. Melatonin levels and rhythms have been reported to be normal in both unipolar depression³⁰⁵ and seasonal affective disorder. (Ferrier & Scott, 1998) However, one study (Wehr et al, 2001) found that the duration of the nocturnal period of active secretion of melatonin was longer in winter than in summer in affective disorder patients but no such changes were found in healthy controls. Excess nocturnal melatonin secretion, possibly related to nocturnal hypoglycaemia, has been reported in untreated females with anorexia nervosa. (Arendt et al, 1992) One meta-analysis (Buscemi et al, 2006) found no evidence that melatonin is effective for sleep restriction (incl. jet lag and shiftwork disorder) or secondary sleep disorders.

A higher brain stem level lesion at the mid-collicular level (A: *cerveau isolé*) is associated with EEG and pupil responses characteristic of permanent sleep; a lesion just above the entry of the fifth cranial nerve (B: *mid-pontine preparation*) leaves the brain permanently awake; and a lesion cutting the brain stem off from the cord (C: *encephalé isolé*) prevents sensory inputs from the cord reaching the brain and is associated with a normal sleep-waking cycle. Therefore, between B and C, there may be a lower brain stem sleep-promoting area, and, between A and B, there may also be a rostral arousal area. There is animal experimental evidence for these suggestions. (Steptoe, 1992) Stimulation of the anterior (ventrolateral preoptic nucleus) and posterior (tuberomammillary nucleus) hypothalamus may induce sleep and wakefulness respectively, illustrating an important cortical role in the sleep-wakefulness cycle. Hence, both brain stem and cortex have important, integrated roles. More recently, it has been determined that a small group of neurones in the posterolateral hypothalamus secrete the neuroexcitatory peptides hypocretin 1 and hypocretin 2 (orexins A and B).³⁰⁶ These neurones project widely throughout the brain, including areas associated with arousal, such as the locus coeruleus, the raphe nuclei, and the thalamus. The arousal produced by hypocretin 1 may occur via activation of histamine-1 receptors. Lesion studies in the rat suggests that cholinergic input from the nucleus basalis in the forebrain is important for suppressing slow wave activity during wakefulness. (Buzsáki et al, 1988)

It has been suggested that REM rebound during drug withdrawal is really subclinical delirium tremens (DTs). Prior to the DTs, the sleep EEG record is almost entirely occupied with REM, suggesting that REM spill over constitutes the DTs. (Scheepers, 1997) The EEG shows *increased frequency* during DTs, hyperthermia and PCP poisoning (*hyperactive deliria*) and reduced frequency in all other deliria. (Mulligan & Fairweather, 1997) While the EEG in most deliria shows diffuse slowing, it can, in practice, be normal or fast with alcohol withdrawal delirium. (Bernstein, 2000)

Sleep may have an immune function, e.g. sleep onset is associated with secretion of interleukins 1 (α and β) and 2. (Tattersall et al, 1998) Interleukins (IL) 6, 15 and 18, nerve and other growth factors, brain-derived neurotrophic factor (BDNF), neurotrophins 3 and 4, tumour necrosis factor, interferons α and γ , tumour necrosis factors α and β , oleamide, prostaglandin D2, nitric oxide, nuclear factor kappa B also promote sleep. Sleep is inhibited by interleukins 4, 10 and 13, prostaglandin E2 and a number of other substances. Rats deprived of sleep for two weeks or more die, probably of infection, although short-term sleep loss may sometimes enhance host defences. (Majde & Krueger, 2002)

Chronobiology is the study of the regular biological rhythms of living organisms. Almost all biological functions have some rhythm and the length of the rhythm varies, e.g. daily (circadian). Examples of rhythms include the sleep-wake cycle, hormonal levels, body temperature, and the menstrual cycle. Rhythms may be in or out of phase with each other. Also rhythms may be phase advanced (brought forward in time) or delayed (brought backward in time). Biological rhythms are set by internal and external zeitgebers (time clues). The main endogenous zeitgeber is the suprachiasmatic nucleus (SCN) of the hypothalamus³⁰⁷. Lesions of the mouse (and other animals) SCN lead to sleep fragmentation and lack of a

preservation of melanopsin (a pigment) receptors in specialised retinal ganglion cells which signal the clock in the hypothalamus (project from lateral geniculate body to suprachiasmatic nucleus [retino-hypothalamic tract]) independent of vision, may protect blind people against free-running, as may work and exercise routines; managed with regular routine, morning bright light (if sighted), nocturnal doses of melatonin (if blind), or perhaps B₁₂.

³⁰⁵ Sleep-related changes in depression (e.g. earlier REM onset and early morning awakening) suggest possible phase advance of internal circadian control system. (Lamont et al, 2007) Other reported changes are increased amount of REM, longer sleep latency, decreased total sleep time, diminished sleep efficiency, and a reduction in slow wave sleep.

³⁰⁶ Orexins are cleaved from preprohypocretin.

³⁰⁷ Paired structure above optic chiasma containing about ten thousand neurones. These are innervated by 5-HT neurones from midbrain raphe nuclei. The first circadian clock was discovered in mimosa plants that continue to open and close their leaves each day despite being deprived of sunlight: this discovery, in 1729, is attributed to Jean Jacques d'Ortois de Mairan (1678-1771), a French

daily sleep/waking rhythmicity. Examples of exogenous zeitgebers are the normal workday, set mealtimes, sunrise and sunset (The *photoperiod*, daily variations in intensity of light, is the chief zeitgeber for synchronizing circadian clocks.).

If a human is removed from all outside clues, his circadian³⁰⁸ rhythms lengthen to 24.5 hours³⁰⁹. Jet lag is important here: if one goes from E to W one experiences a phase delay which is less of a problem than the phase advance (shortening) associated with travelling from W to E. The latter represents the opposite of the natural tendency to lengthen the biological day. Biological rhythms are disrupted by shift work.³¹⁰

Depression is associated with early morning wakening (EMW³¹¹), reduced REM latency, and neuroendocrine abnormalities, all of which may be due to lack of co-ordination in biological rhythms.

Exposure to artificial light for seasonal affective disorder or changing the sleep-wake cycle (as in sleep deprivation) may ameliorate symptoms. Lithium, tricyclics, and MAOIs delay rhythms in animal studies.

Some depressives might have phase-advance disorders.(Robash & Hall, 1989)

*Clock genes*³¹², mainly found in the SCN, can maintain a circadian rhythm of transcription in constant darkness and can be entrained to a new light/dark cycle when exposure to light occurs. A cycle occurs of protein production which then inhibit transcription, degradation of these proteins, followed by further transcription. The SCN gets information from retinal photoreceptors via the (monosynaptic) retino-hypothalamic tract. It also gets photic and non-photoc information from the lateral geniculate nucleus, as well as non-photoc data from median raphe, ventral subiculum, and infra-limbic cortex. Anticipation of food delivery, arousing activity (running on a wheel), and deprivation of sleep are known *zeitgebers*³¹³ in rodents.(Sinton & McCarley, 2003, p. 371)

Hibernation, a state of internally controlled hypothermia, is not true sleep. Birds sleep, even on one leg.

Cows sleep with their eyes open (as can humans) and meanwhile continue to chew the cud. Different species normally sleep by night (humans) or by day (cats, rats).

While awake, we experience increased adrenaline and corticosteroid output³¹⁴, increased physical activity and relatively poor healing. During sleep there is increased output of testosterone and growth hormone³¹⁵.

Cholinergic activity is at its highest during REM sleep, and the aminergic cells (serotonin and noradrenaline) are at their least active during this time.(Craggs & Carr, 1992) In fact, acetylcholine can promote cortical activation that can accompany the waking state or REM sleep. It also reduces muscle tone via the brainstem. Whilst REM is eliminated by lesioning the cholinergic ponto-mesencephalic neurones

astronomer. The fact that these plants carry out these actions every 22 hours when in constant light was recorded in 1832 by Augustin Pyrame de Candolle (1778-1841), a Swiss botanist and physician.

³⁰⁸ L. *circa*, roughly; *dies*, day, i.e about a day long. Circadian rhythms have a **mean** (level at which the oscillation takes place), a **period** (time to complete a cycle), an **amplitude** (distance between mean and peak of cycle's oscillation), and an **acrophase** (time of the peak of the circadian rhythm's phase). **Masking** or **masking effect** refers to the influence of environmental factors (temperature and light intensity and duration, food, social activities, etc) and internal states (e.g. hunger, sleep, fatigue, movement, etc) on the shape of endogenous rhythms.

³⁰⁹ This period may be genetically determined. Researchers have bred hamsters with different innate circadian rhythms (20-25 hours) – if the suprachiasmatic nucleus is transplanted from one hamster to the other the recipient's rhythm changes to that of the donor.(Ralph ea, 1990)

³¹⁰ Beware the hours worked during internship! Shift workers appear to adapt less well than do people who traverse multiple time zones. Journeing home in daylight (which is much brighter than office lighting) interferes with adaptation.

³¹¹ **EMW** is also associated with mania, alcohol, caffeine, anorexia nervosa, and ankylosing spondylitis (pain).

³¹² E.g. *clock*, *timeless*, and *period (PER)* genes. Polymorphisms of *PER2* and *PER3* were discovered in familial advance sleep phase disorder and in delayed sleep phase disorder respectively. There have been conflicting reports of a *CLOCK* gene polymorphism in people who prefer evenings (owls).(see Lamont ea, 2007) Most cells contain circadian clocks and such clocks are set by endogenous signals. Such signals induce a second messenger cascade leading to altered concentration concentration of clock gene products. The molecular clock then regulates the rhythmic expression of genes or other functions of cells, e.g. hormonal secretion or membrane electrical characteristics.(Roenneberg & Mellow, 2005) The intrinsic oscillations of cells are synchronised by the SCN. An important output target of the SCN (via the paraventricular nucleus) is the pineal gland (source of melatonin).

³¹³ Non-photoc synchronisers. The term 'social zeitgeber' has been used for social factors that entrain biological rhythms, e.g. occupational and interpersonal demands. *Zeitstörers* are events that disturb biological clocks. They include social, chemical, and physical events, e.g. the nocturnal demands of the newborn on its carer, long haul flights, erratic meals/sleep, rotational shift work, working late to meet deadlines, and daylight saving time changes to the clock. The social zeitgeber theory is still some distance from proven fact.(Grandin ea, 2006) In other words, for example, lack of sleep may be an early symptom of mania or may precipitate mania in someone with a genetically unstable suprachiasmatic nucleus as much, or more, as lack of sleep can cause mania.

³¹⁴ Cortisol plasma levels are highest at about 6 a.m. and lowest in late afternoon or evening.

³¹⁵ Growth hormone is released in pulses throughout the day, but pulses are more closely spaced during the first hours of sleep than at other times.

(but with little effect on waking), damage to the cholinergic neurones in the forebrain causes deficits in attention and activation of the cortex during the waking state. Locus coeruleus neurones discharge at their fastest rates during waking³¹⁶, at a slower rate during slow wave sleep, and are quiet during REM sleep; this is very similar to the effects of both histamine and serotonin. Serotonin (5-HT) promotes a quiet, relaxed but waking state that facilitates sleep; damage to the raphe nuclei may lead to complete insomnia with agitation. Dopamine mainly promotes wakefulness, but it is active during sleep during positive (awarding) emotional states. Glutamate is an excitatory neurotransmitter that seems critical for the waking state, and is the transmitter of the ascending reticular activating system.(Jones, 2002) Orexins A and B³¹⁷, from hypothalamic neurones, stimulates feeding and wakefulness.

Substances that promote or permit REM sleep include acetylcholine.³¹⁸ Interestingly, reserpine increases REM in depression, possibly because of a depression-related lack of monoamines. Vasoactive intestinal peptide is often cotransmitted with acetylcholine and also appears to promote REM. Gamma-aminobutyric acid (GABA) may contribute to muscle atony, as may glycine may also contribute to atony.³¹⁹ Noradrenaline, serotonin, and histamine neurones are turned off during REM. Dopamine possibly contributes to some aspects of dreaming: vivid dreams have accompanied hallucinatory states in people taking amphetamines³²⁰ or L-DOPA. Cholinesterase inhibitors can also cause vivid dreams. Glutamate may also be involved in REM sleep.

Slow wave sleep³²¹ (SWS) is promoted by GABA³²², growth hormone-releasing hormone, somatostatin³²³, adenosine³²⁴, and, acting via the tenth cranial nerve when released in association with alimentary activity, insulin, cholecystokinin and bombesin.

After a true epileptic seizure there is an increase in the serum prolactin, which does not occur following a pseudoseizure; there is also a rise in the serum cortisol but this is much less specific. Attacks of bronchial asthma commonly occur at night because of exaggerated bronchial constriction and may cause insomnia; the sole symptom may be a cough; some cases of insomnia are secondary to management with adrenergic agents; fatalities are most likely among those whose peak expiratory flow rate fall the furthest.(Williams ea, 1988; Catterall & Shapiro, 1993)

We live in a world of sleeping tablets. At 65 years of age 50% of females regularly take a sleeping pill.

Neurotransmitter control of REM sleep

Noradrenaline:	↓ REM + increased wakefulness
Acetylcholine:	↑ REM (? depressives supersensitive to ACh)
↓Serotonin (5-HT):	↓ REM (↓1-tryptophan: ↓ REM ³²⁵)

³¹⁶ Especially if something arouses the subject.

³¹⁷ Also called hypocretins 1 and 2 respectively. They are secreted during the day and suppress the ventrolateral preoptic area (VLPO).

³¹⁸ Eserine, which blocks acetylcholine breakdown, normally promotes waking, but it leads to REM if monoamine levels have first been depleted by reserpine. Reserpine depletes transmitters in storage vesicles by blocking transmitter uptake by magnesium-dependent ATPase-linked transport sites on vesicle membrane, so making transmitter available for catabolism.

³¹⁹ Locally applied strychnine reverses the atony of REM by blocking glycine.

³²⁰ Mice deprived of dopamine transporter (knockout) are insensitive to wake-promoting effects of amphetamine.(Staner, 2005)

³²¹ **Stages 3 and 4 of non-REM sleep**, also called delta sleep. The sleeper is pale and peaceful, heart and breathing are slow, and it is difficult to rouse him/her. Sudden waking during SWS is associated with transient confusion (**confusional arousal**) with simple, non-affect laden motor behaviour. Speech may be indistinct, behaviour automatic, and response to the environment is reduced. Memory for the event is very poor. There may be delta waves on the EEG. Confusional arousals may occur during daytime naps. *Sleep drunkenness* (inertia following on final awakening), *sexsomnia* (abnormal sexual behaviour), and *sleep-related violence* may be seen as variants of confusional arousals.

³²² Benzodiazepines act via GABA-A receptors to open chloride channels. Gamma-hydroxybutyric acid (GBH) acts on GABA-B receptors to open potassium channels and promotes SWS and REM.

³²³ And the related peptide cortistatin.

³²⁴ **Adenosine** promotes SWS through direct inhibitory effects on cholinergic basal forebrain neurones; it also stimulates the indirectly.ventro-lateral preoptic nucleus. Adenosine receptors are antagonised by caffeine. Adenosine levels increase during wakefulness and decrease during sleep.

³²⁵ If a rich large neutral amino acid drink without tryptophan is given to someone treated with SSRIs (but not selective noradrenaline reuptake inhibitors) for depression a transient increase in depression follows after a few hours, something that does not happen in untreated cases. This is due to removal of tryptophan from stores as a result of stimulation of protein synthesis, for which tryptophan is required.(Checkley, 1998) Only 1-2% of body tryptophan occurs in brain and, since serotonin does not cross the blood-brain barrier, the brain must make its own 5-HT. Tryptophan competes with other amino acids for transfer across the blood-brain barrier by LNAA (large neutral amino acid) transporter. Male brain makes more 5-HT than female brain under normal circumstances, and this gap

Ancillary tests in psychiatry

Many different tests come under this heading. Examples are blood and urine tests, drug assays³²⁶, radiological examinations (skull, chest, etc.), cerebrospinal fluid (CSF) examinations³²⁷, angiography, myelography, electroencephalography (EEG), visual evoked responses, electromyography, nerve conduction studies, muscle biopsy, computerised axial tomography³²⁸ (CT), positron emission tomography (PET), and nuclear magnetic resonance (NMR – because of the association of ‘nuclear’ with bombs, NMR is now called magnetic resonance imaging, MRI). The clinical application of neuroimaging in psychiatry is still developing.(Sharma & Sheringham, 2002) We are still not certain about the nature of the in vivo competition between endogenous and exogenous ligands,(Liddle, 2001, p. 14) and the use of different exogenous ligands may be partly responsible for the failure of different investigators to produce compatible results. Biopsy is occasionally required in the interface between neurology and psychiatry in order to reach a diagnosis: brain/meninges, pharyngeal tonsil (vCJD), nerve, or muscle. It is important that specimens are seen by an experienced neuropathologist.

The TRH challenge test is performed by giving 500 µg TRH and then measuring TSH at 15, 30, 60, and 90 minutes. A blunted TSH response has been recorded in, amongst others, depression, anxiety, and bulimia nervosa. A blunted growth hormone response to insulin challenge has been reported in depression. The dexamethasone suppression test (DST), first used to assess cases of Cushing’s disease, is discussed with the affective disorders.

Hypoalbuminaemia³²⁹ reduces drug-carrying capacity for protein-bound medications leading to a rise in free drug serum concentrations despite therapeutic range levels for total serum levels. Low serum albumin levels may be of aetiological significance in confused patients.

The term *tomogram* simply means viewing something in layers or planes. Neuroimaging techniques may be structural as with CT or MRI, or functional as with SPECT or PET. All brain-imaging techniques utilise computers to construct a series of 2-dimensional slices from a succession of one-dimensional data.

Regarding imaging, functional segregation of parts of the brain has helped understanding of symptoms, but functional integration is better for understanding fundamental disease mechanisms.(Dolan & Friston, 1997)

There are many potential tests of arousal: paper and pencil tests such as Thayer’s Activation-Deactivation Adjective Checklist, cardiovascular status (pulse rate, blood pressure, skin blood flow, forearm blood flow), electrodermal activity (galvanic skin response), breathing rate, electromyography, electroencephalography (not very useful), pupillary diameter, genital arousal, and biochemistry (e.g. adrenaline at the extreme level of arousal). Such measures must be integrated with the complete clinical picture, mindful of individual idiosyncrasies. Arousal is best gauged using a number of measures.

Skull radiography

The yield of helpful findings is fairly low in psychiatry. A single lateral film is usually adequate unless specific pointers suggest further work. Skull fractures may not have been suspected. Infection (e.g. from mastoid or ear) may destroy bone. Meningiomata may erode bone or cause bony overgrowth, the internal auditory meatus³³⁰ may be eroded by a neuroma, abnormal vascular marking may mean tumour (including vascular tumour), osteolytic lesions may infer multiple myeloma or multiple metastatic deposits, and the skull may appear generally thick or woolly in osteitis deformans. The posterior clinoid processes are eroded by increased intracranial pressure³³¹, and the pituitary³³² fossa (sella turcica: ‘Turkish saddle’) can be

widens with tryptophan depletion.(Svensson & Mathé, 2002) Tryptophan depletion may unmask an underlying serotonin-related trait dysfunction in persons prone to major depressive disorder.(Neumeister ea, 2004)

³²⁶ E.g. the presence of cocaethylene in serum suggests combined use of cocaine and ethanol.

³²⁷ CSF recovered at lumbar puncture (LP) should normally be very clear and not coloured with a (recumbent) pressure of 60-150 mm of CSF; there should be less than 5 cells per cubic millimetre (only mononuclear cells should be present); there should be no oligoclonal bands; blood should be taken at the same time and CSF glucose should be 66-50% of blood glucose; and IgG should make up less than 15% of total protein in CSF.

³²⁸ Gk., *tomos*, cut. CT images can only be viewed in the axial plane, unlike MRI which produces axial, saggital, and coronal images.

³²⁹ Malnutrition, liver and kidney diseases, chronic diseases, the elderly, etc.

³³⁰ Various neural foramina may be expanded by tumours, e.g. optic.

³³¹ There may be a ‘beaten silver’ appearance to the vault.

³³² The anterior pituitary is derived from an upgrowth of Rathke’s pouch (a depression in the roof of the developing mouth). This meets a pouch of the floor of the third ventricle which becomes the posterior pituitary. The ‘empty sella’ syndrome is usually a result of flattening of a normally functioning pituitary.

enlarged from within or above. Half of all adults have a calcified pineal gland, which may be displaced by a pathological process. Other structures may also show calcification, such as the falx cerebri and the choroid plexuses, and, sometimes, parts of a tumour. Calcification can occur in the walls of an aneurysm or an angioma, in tubers of epiloia, and in the basal ganglia in the case of excessive parathormone levels.

*The electroencephalogram*³³³ (EEG)

The EEG, an indirect measure of brain activity, measures summation of electrical activity. This is recorded as a difference in electrical potential between two active recording electrodes³³⁴. The weak signal requires amplification. In a standard recording, the paper moves at 30 mm/sec and an impulse of 50 μ V causes the pen to deflect by 7 mm (there may be no paper sheet, as in digital EEG). The standard arrangement for EEG electrodes (usually the International 10-20 System) are named for the underlying brain lobe³³⁵. (Reeve, 2003) Cycles per second are synonymous with *Hertz* (Hz). Common EEG rhythms are subdivided according to frequency (see box). Rhythmic changes of potential are seen of about 20-40 millionths of a volt. These are produced by the inhibitory and excitatory postsynaptic potentials on neuronal dendrites close to the surface of the brain. At any moment only 3% these neurones contribute to the detected signal. By convention, EEG recordings are arranged so that negative potentials cause an upward deflection.

EEG rhythms³³⁶

<u>Activity</u> ³³⁷	<u>Hz</u>	<u>Usual location</u>
Alpha (α)	8-13	posterior
Beta (β)	> 13-30	anterior
Theta (θ)	4-7.9	generalised +/- focal
Delta (δ)	0.4-3.9	generalised +/- focal
Gamma (γ)	> 30	

Alpha, best seen over the occiput, is the dominant/background EEG activity in normal people. It is prominent when in a relaxed state with the eyes closed or during hypnosis, (Craggs & Carr, 1992) but disappears with eye opening, concentration, or anxiety. Since its presence accurately monitors freedom from anxiety it is useful in biofeedback, 'alpha-training', and other behaviour modification techniques. Alpha rhythm is also lost during sleep or with psychotropic drugs and it slows in old age and in almost every neurological illness.

Beta rhythm is usually of lower voltage than alpha, is present normally, but increases with concentration, anxiety, or minor tranquillisers; it replaces alpha rhythm during stimulation or when the eyes are opened; best seen over mid-scalp (somatosensory/motor cortex). Tolerance does not occur to benzodiazepine-induced fast beta activity.

Theta & Delta are usually absent in healthy, alert adults, are a normal finding in children, in everyone as they enter deep sleep, and in many people with fairly minor problems, e.g. migraine headache. If diffusely present over the brain, slow activity may indicate a degenerative or metabolic disorder, but, when localised, may indicate a discrete cerebral lesion, but its absence does not exclude such a lesion.

Mu rhythm, found in the precentral region, lies within the alpha range and is reduced by moving (or thinking about moving) the contralateral limbs. *Lambda waves* are caused by small eye movements. They resemble the teeth of a saw and are usually situated over the occiput. *Gamma rhythm* (up to 100 Hz) are thought to represent the coming together of different neuronal networks to allow cognition or movement. Autism has been associated with increased amplitude in this frequency and may represent diminished inhibitory processes whereas schizophrenia may be associated with differences in gamma amplitude and

³³³ Hans Berger of Jena introduced the human EEG in 1929: the Nazis prevented him accepting the Nobel Prize (he hung himself). (Finger, 2000)

³³⁴ One cannot record from a single electrode.

³³⁵ E.g. Fp1 or left frontal pole, P4 or right parietal, C means along a central line between the ears, Fz is frontal along the vertex or a line from nose to occiput, and Pg 1 and 2 are left and right nasopharyngeal, etc.

³³⁶ Exact frequencies vary slightly with reference source. Beta frequency range is sometimes divided into beta 1 (13-20 Hz), beta 2 (21- or 35 Hz) and gamma (> 30 or 35 Hz). The study of the gamma band is relatively new and followed discovery of its functional significance in intracerebral recordings.

³³⁷ In summary, delta = sleep, theta = drowsy/hypoaalert, alpha = relaxed wakefulness, and beta = alert and vigilant.

coherence.(e.g. Light ea, 2006) *Coherence* refers to a comparison of the periodicity of a particular frequency between two locations and research using analysis of coherence suggests that circuitry is abnormal in Parkinson's and Alzheimer's diseases.

In most instances EEG recordings are taken via scalp electrodes. Sphenoidal electrodes (less often used today than heretofore) record discharges from the temporal lobes. One reason for this decline in use is the belief that this technique may simply sharpen an already discernible but muffled surface EEG abnormality. Electrodes are pushed through the masseter muscle and up behind the zygomatic arch, whereas in the simpler nasopharyngeal EEG the electrodes are placed via the nose in the pharynx against the floor of the sinus. Nasopharyngeal leads are not thought to add much to scalp recordings and can be very uncomfortable. Although electrodes F7 and F8 are known as anterior temporal leads they lie over frontal areas; nevertheless, they reflect mostly anterior temporal lobe activity. More accurately, anterior temporal activity can be recorded by tracing a line between the external meatus and lateral canthus and putting the electrode one cm above a spot one third of the distance forward from the meatus.(Homan ea, 1988)

Anterior temporal leads as just described are about as sensitive as nasopharyngeal leads and, arguably, a combination of anterior temporal and nasopharyngeal leads may be as sensitive as sphenoidal leads.(Goodin ea, 1990) During surgery it becomes possible to record directly from the surface of the brain (electrocorticography³³⁸). Depth electrodes³³⁹ record activity from specific structures within the brain.

During surgery it becomes possible to record directly from the surface of the brain, so-called electrocorticography.

Activating procedures, to detect or enhance abnormalities, include sleep (may be chemically induced³⁴⁰), deprivation of sleep, flashes of light using a stroboscopic light (photic stimulation³⁴¹), hyperventilation³⁴², metrazole³⁴³ (Cardiazol), pentylenetetrazol, chlorpromazine, 24-hour monitoring, cortical electrodes at surgery, and so on. Prolonged monitoring may take the form of videotelemetry (video of patient plus EEG) or ambulatory monitoring (no visual accompaniment).

Spike and wave patterns³⁴⁴ are nearly always pathological, e.g. the classic finding in petit mal epilepsy is 3c./sec. spike and wave discharges. Abnormalities can be focal³⁴⁵, unilateral or generalised. They can be synchronous or asynchronous, depending on whether they appear in corresponding leads. EEGs can be normal in people with abnormalities and vice versa. About 10% of people have EEG 'abnormalities', usually mild. An example is the normal hunger striker with hypoglycaemia. The EEG rarely offers a specific diagnosis. Even the localisation of an abnormal electrical discharge is not a universal indicator of lesion site.

Many 'functional' psychiatric disorders are associated with EEG abnormalities. Hill (1952) found that psychopaths (especially those with a history of impulsive homicide) had evidence of 'delayed' cerebral maturation (bilateral rhythmic theta activity in central and temporal regions, alpha variants, and episodic posterior temporal slow-wave foci). The latter may improve both in terms of EEG tracing and in behaviour, with age. In practice, about half of psychopaths presenting to an acute psychiatric service will have an abnormal EEG, a finding that shows a negative correlation with age and a positive one with the occurrence of epileptic convulsions. Theories about the origin of delays in EEG maturation range from environmental deprivation to epilepsy or various 'organic' diatheses. The finding of slow waves should not be too readily passed of as indicative of 'electrical immaturity'.(Fenwick, 1992)

Decreased slow-wave sleep has been reported to correlate positively with increased negative symptomatology in young medication-naïve schizophrenic patients. (Ganguli, ea, 1987) During the performance of left hemisphere cognitive activation tasks it is possible to show a significant increase in

³³⁸ Using the electrocorticograph or EcoG the hope is to be able to map epileptogenic circuits in cases of TLE.

³³⁹ These have been implicated in the transmission of Creutzfeldt-Jakob disease (characterised by periodic sharp wave bursts on scalp EEG).

³⁴⁰ IV thiopental induces beta activity (less so over damaged temporal areas), characteristically with runs of spindles.

³⁴¹ Generalised spike and wave response to light is common in generalised epilepsy but rare in localisation-related epilepsy.

³⁴² Causing cerebral hypoxia by local vasoconstriction due to carbon dioxide depletion – may cause problems in cases of cardio-/cerebro-vascular disease or sickle cell disease.

³⁴³ A synthetic soluble derivative of camphor.

³⁴⁴ Although spikes and sharp waves are usually followed by slow waves, the term 'spike and wave complex' generally infers a very prominent slow wave that has a higher amplitude than the spike. *Spike and wave formations are found in 2% of people who do not have epilepsy.*

³⁴⁵ **Focal lesions** may be associated with localised EEG disturbance or a disturbance located at a distance from the lesion or with a generalised disturbance.

alpha (α) coherence in areas related to left focal frontal sites, but, in the Morrison-Stewart ea (1991) study schizophrenic patients did not show the same degree of focal activation of left frontal areas, which may reflect aberrant functional brain organisation, especially affecting the left hemisphere. The testing condition that has most consistently revealed hypofrontality³⁴⁶ (prefrontal cortical hypofunction) in schizophrenia is the Wisconsin Card Sorting Test. (Weinberger ea, 1986; hypofrontality is also associated with depression, regardless of cause: George ea, 1993) Perhaps due to partial failure of localised cerebral autonomy, the EEG in schizophrenia is excessively synchronous between temporal areas. (Flor-Henry & Yeudall, 1979) Maixner ea (1998) tested schizophrenic patients while medication-free and after a few weeks on antipsychotic medication. Sleep continuity improved consistently. REM³⁴⁷ latency increased, but one-third of individuals continued to exhibit short REM latencies of less than 60 minutes. Stage 3 sleep increased, while stage 4 remained unchanged. The authors wondered if shortened REM latency and disturbed sleep continuity may be reversible state markers, with reduced slow wave sleep representing an irreversible trait abnormality in schizophrenia. Harris ea (1999) used the so-called 'quantitative EEG' (qEEG) and found that 'psychomotor poverty' was associated with both delta and beta power, and 'reality distortion' was associated with alpha-2 power; no significant correlations were found between the positive and negative syndrome dichotomy and the qEEG. Kwon ea (1999), using auditory stimulation at different rates (20-40 Hz) and measuring synchronization of the EEG, found reduced EEG power at 40 Hz in people with schizophrenia. This, they suggested, might reflect dysfunction of the recurrent inhibitory drive on auditory neural networks.

qEEG³⁴⁸

Quantitative analysis of EEG in time, frequency, and space domains

Can detect changes that the eye cannot see

Changes in brain function reflected in amplitude, frequency, and topography

Computerised EEG topography (CET, qEEG mapping)

Construction of 2- or 3-dimensional matrix for topographic representation of qEEG parameters, e.g. instant amplitude and band power

Colour-coded maps were developed from the late 1980s

Low-resolution electromagnetic tomography (LORETA)

Allows localisation of electrical sources of surface field in 3-dimensional brain space

An *event-related potential* (ERP) is a recording of brain electrical activity linked in time to an event (such as an auditory stimulus). Components of an ERP may be positive (P) or negative (N) depending of the direction of deflection of the electrical stimulus. Numbers are an average of the time in milliseconds passed between stimulation and appearance of a component, e.g. P300³⁴⁹ or N400. The early components (< 150 msec.) derive from aspects of the stimulus, such as loudness. Later components derive from the cognitive workings (e.g. updating of memory within present context in the case of the P300) or the extent to which a stimulus is unexpected given the context (N400). The P300 latency is prolonged in depression and reflects a diminished ability to attend, which in turn may be dependent on serotonin. The P50³⁵⁰ is thought to index early gating of incoming sensory data (abnormal in most, but not all, schizophrenic subjects; also abnormal in their clinically healthy relatives; linked to polymorphism in alpha-7 nicotinic receptor).

Mismatch negativity (MMN)

An ERP sensitive to change in a stimulus during an otherwise repetitive pattern

³⁴⁶ Hypofrontality in schizophrenia is a rather contentious issue with many methodological caveats. (McKenna, 2007, p. 129)

³⁴⁷ Aserinsky and Kleitman discovered REM sleep in 1953.

³⁴⁸ See Gruzelier ea. (2002)

³⁴⁹ Synonymous with P3, the third positive potential, which happens to occur 300 msec after the stimulus.

³⁵⁰ The P50, a positive deflection recorded by scalp electrodes 50 msec after an audible click, is generated in several parts of the human brain including the pyramidal cells of the hippocampus. Researchers have looked at P50 abnormalities as a potential endophenotype for schizophrenia. When 2 clicks separated by 200 msec are presented the patient the amplitude of the P50 wave following the second click should be smaller than that after the first click. In some cases of schizophrenia both waves are of equal amplitude, indicating a possible failure of sensory gating. To some degree this abnormality may be related to polymorphisms in or near the alpha-7 nicotinic receptor subunit gene (chromosome 15). Also, atypical antipsychotics are said to equalise the second P50 wave.

Reflects echoic memory (i.e. storing auditory stimuli) operations
 Arises from primary auditory cortex
 May reflect NMDA channel current influx in cortical layers II and III
 While attention may influence MMN somewhat, it is usually assumed to be uninfluenced by cognitive operations
 Salisbury ea (2003, p. 304) state that MMN is preconscious (unlike the P300 which reflects ‘an updating of the conscious information processing stream and of expectancy’)
 Salisbury ea (2002) reported pitch deviant MMN to be reduced by 47% in chronic schizophrenia along the sagittal midline but not in first episode schizophrenia
 Light and Braff (2005) found MMN deficits and their relationship to poor functional status to be stable over time in chronic schizophrenia

Edlund ea, (1987) described 6 cases of atypical panic attacks (hostile, irritable, severe derealisation, and social withdrawal) most of whom had temporary EEG abnormalities, albeit not sufficient to make a diagnosis of temporal lobe epilepsy (TLE), and some did well on carbamazepine or alprazolam.

Wiedemann ea (1999) reported EEG findings in panic disorder suggestive of right frontal overactivity associated with an overactive avoidance-withdrawal system and disturbed cortical processing. Most sleep studies of panic disorder report normal sleep architecture, including normal REM latency. Some panic attacks occur at night, especially during the transition between stages 2 and 3 when dreaming is absent and cognitions are minimal. (Stein & Uhde, 1998) By way of contrast, night terrors appear in stage 4 whereas REM sleep behaviour disorder and nightmares occur during REM sleep.

As demonstrated in 1965 by Shagass, EEG changes following ECT take about two months on average to normalise.

TLE is often characterised by spike discharges over the temporal region but up to half of recordings may be normal; the percentage of abnormal returns may be increased with sphenoidal electrodes in a sleeping patient. In a waking interictal EEG lasting 30 minutes, some 35% of epileptics consistently exhibit epileptiform discharges, 15% never do so, and 50% do so occasionally. (Ajmone Marsan & Zivin, 1970) The yield of relevant diagnostic information from a single waking EEG in a population with epilepsy is about 50%, but with repeated recordings it approaches 85%. A superior yield is achieved with sleep recordings: grand mal seizures are activated in n-REM sleep, and absences or minor seizures may be seen during REM sleep. (Morgan, 1993) Simple ictal phenomena such as déjà vu or a peculiar abdominal sensation are usually associated with an unaltered scalp EEG, i.e. the EEG may be normal during a clinically obvious focal seizure. Epilepsy should never be diagnosed from the EEG alone: there must be a clinical history of seizures. In rare cases, performing the EEG when the patient is doing what he says brings on an attack (e.g. phlebotomy, bathing, standing up quickly, reading) may change a diagnosis to one of epilepsy. The relatives of epileptics often have EEG abnormalities. (Fenwick, 1992)

After cranial trauma, an abnormal EEG may distinguish between behavioral psychogenic and organic problems. However, neuroimaging has largely replaced the EEG when searching for structural lesions. In dementia, the severity of EEG abnormality may not relate so much to intellectual status at the time of the recording as to the rate of progress of the disorder. The EEG in Pick’s disease may reveal little in the way of abnormality. A normal EEG in a depressed individual who has other evidence of possible dementia is suggestive of depressive ‘pseudodementia’ (syn. ‘dementia syndrome of depression’). The more severe a case of Tourette’s syndrome the more qualitatively abnormal the EEG, especially characterised by excess generalised theta activity. (Hyde ea, 1994)

The EEG in sleep

Methods of studying sleep in the Sleep Laboratory include all-night polygraph (polysomnography) recordings, e.g. EEG; ECG; electromyogram (EMG³⁵¹: - the throat muscles are tense, with lots of small electrical spikes, in orthodox sleep, and relaxed in paradoxical sleep); electro-oculograph (EOG: - small, transmitted brain potentials are seen in orthodox sleep; more obvious variations are seen in REM sleep); pulse oximetry (records blood oxygen saturation); respiratory effort recording (nasal and oral airflow using

³⁵¹ Usually recorded submentally.

nasal thermistors plus thoraco-abdominal movement using strain gauges/inductive pethysmography); and snore monitor (microphone on side of neck). Most people have a number of brief awakenings during sleep but may not recognise them as such unless they persist for more than a couple of minutes. Humans tend to take all the day's sleep in one go (100% consolidation) whereas guinea pigs sleep in short bouts spread throughout the 24-hour period.

Non- rapid eye movement (n-REM sleep, orthodox, synchronised) sleep

This makes up the majority of sleeping time. Everything slows down, progressively with deepening sleep. Its 4 stages take about 90 minutes to complete.

Non-REM sleep stages

Stage 1 - starts when sleep starts (low voltage, fast waves – drowsiness, *slow rolling eye movements*: < 0.5 Hz)

Stage 2 - associated with K-complexes³⁵² and sleep spindles (spindles of 14c./sec. activity: brief episodes of fast activity)

Stages 3 and 4 (slow wave³⁵³ [SWS] or delta sleep) - deepest levels of sleep, with high amplitude slow-waves

After falling asleep, the normal person first enters n-REM sleep (each phase lasting 60-90 minutes). Each n-REM phase is interrupted by REM phases lasting 12-20 minutes). Throughout sleep there is progressive decline in SWS³⁵⁴ with an increase in the proportion of REM across successive REM/n-REM cycles.

REM (paradoxical, desynchronised) sleep

The term 'paradoxical' refers to the fact that the associated physiological measures (including the EEG), relative to non-REM and apart from hypotonia, are suggestive of an alert (active cortical) state. Bursts of conjugate rapid eye movements are seen in anterior leads. In young adults, about 25% of the night is spent in this stage (75% in non-REM: 5% in stage I, 45% in stage II, 12% in stage III, 13% in stage IV), up to one-half in infants (neonate goes straight into REM; by 4 months the pattern shifts so that REM is reduced to less than 40% of sleep time and there is an initial non-REM period; sleep spindles appear at 3-4 months), and with a slight reduction (in both REM and slow-wave sleep) in the elderly. The sleep cycle does not lengthen until adolescence, when the 90-minute cycle of the mature adult is achieved.(Anders, 1996)

REM sleep

Mostly packed toward the second half of the night

Becomes more frequent and lasting longer as sleep continues

Most, but not all, dreaming found here

EEG: low voltage, fast activity (alpha activity is present but slower than when awake)

Spontaneous penile erection³⁵⁵

Poikilothermia - no response to changes in ambient temperature

Increased metabolic rate/autonomic arousal - increased brain temperature, oxygen consumption, and blood flow, varying tachycardia, and sharp and frequent changes in respiration (irregular breathing) and blood pressure

Reduced ventilatory response to CO₂

Cardiac irregularities may occur³⁵⁶

No EMG activity

Apart from some twitching (of small muscles: hands, feet and face) the body is flaccid (with postural hypotonia) – extraocular, diaphragmatic and middle ear muscles are not inhibited

³⁵² Number of K-complexes and sleep spindles decrease with age. **K-complexes** are said to resemble the letter K: high amplitude biphasic waves, the first component being negative. K-complexes can be invoked during light sleep by ambient noise and may represent efferent cortical signals that travel to thalamus and brain stem. The **spindles** are complexes of increasing and then decreasing amplitude (12-14 Hz). They occur in short bursts and may be involved in cortical inhibition. They are found in stages 2 to 4 of non-REM sleep although they are masked to a large degree by other waves in the latter two stages.

³⁵³ Slow wave sleep declines with age (especially in males) leaving the majority of non-REM then consisting of stage 2.

³⁵⁴ I.e. non-REM stages 3 and 4 are mainly found early in the sleep period. There may be no SWS in the last cycle.

³⁵⁵ In males of all ages. Ejaculation occurs in response to dreams of a sexual content but the erection as such is content neutral. Clitoral erection also occurs in REM sleep.

³⁵⁶ Angina may occur on lying flat (decubitus angina) or during vivid dreaming (nocturnal angina).

Sleep becomes shallower as sleep progresses
Final REM period usually coincides with waking

In 'endogenous' depression (Kaufman, 1985) the first REM period is brought forward and is very long and intense; total REM is almost the same as normal but is mostly packed into the first part of the night, leaving very little REM for later; and the patient wakes early (EMW) and may experience increased sleep latency³⁵⁷. In 'major' depression there is increased sleep-onset latency, reduced total sleep time and sleep efficiency³⁵⁸, reduced percentage of total sleep time spent in stages 2 and 3, and reduced REM latency (comes on earlier) with increased REM density (longer time spent in REM). (Mendlewicz & Kerkhofs, 1991) From a diagnostic viewpoint, about 15% of depressed patients have normal or even prolonged REM latency³⁵⁹ and sleep deprivation, narcolepsy, and medical illnesses can also cause these phenomena. Also, depressives have their temperature nadir advanced by some hours and have an earlier secretion of both cortisol³⁶⁰ and the noradrenergic derivative MHPG. Therefore they experience a phase shift advance, the normal circadian rhythm having been brought forward in time. Neurons generating REM sleep are found at the ponto-mesencephalic junction. After a few sleepless nights a person becomes confused, incoherent and irrational. The amount of REM sleep is increased by LSD25, reserpine (a depressogen), thalidomide, γ -hydroxybutyrate³⁶¹, nefazodone, possibly by an effect on 5-HT_{2A} receptors, (Delgado & Gelenberg, 1996; Buysse ea, 1996; Leonard, 1997) and bupropion. (Buysse ea, 1996) Cholinesterase inhibitors increase REM in Alzheimer patients³⁶². (Morales Wdos ea, 2006) REM is decreased by MAOIs³⁶³, tricyclic antidepressants (TCAs³⁶⁴), amphetamines, alcohol³⁶⁵, clonidine³⁶⁶, barbiturates, and large doses of benzodiazepines (BZD). Agomelatine does not suppress REM sleep. When REM suppressers are discontinued, there is REM rebound with insomnia and nightmares, which may last for several weeks. SSRIs and venlafaxine reduce the amount of REM sleep. Fluoxetine disrupts sleep continuity. Interestingly, combining fluoxetine with the hypnotic drug eszopiclone was associated with greater improvement in depression scores than when fluoxetine was given alone, and such improvement was not explained by better scores on sleep items within the depression scales. (Fava ea, 2006) SSRIs can cause insomnia and, when stopped too quickly, nightmares. While benzodiazepines initially reduce REM sleep there follows, after a week or so of adaptation, a return to a normal total REM time. If the drug is then stopped, there will be increase in REM to above pre-treatment levels (rebound, perhaps with nightmares) which slowly (up to 6 weeks max.) returns to baseline. (Cooper, 1995) In summary, BZDs increase total sleep time and the number of REM cycles (increased number of dreams) and decrease sleep latency, awakenings, all 4 stages of non-REM sleep, and total REM sleep. (Ballenger, 1998) Excess fast beta activity anteriorly on the EEG is suggestive of BZD or barbiturate consumption. Modafinil has minimal effect on sleep architecture when used in therapeutic doses but the high doses employed by the military presents sleep; when the soldier eventually sleeps the EEG is the same as for non-drug-induced sleep deprivation. Oxybate reduces fragmentary REM occurrence in narcolepsy.

The nadir (lowest point) of body temperature occurs in the second half of sleep; maximum body temperature occurs in the afternoon. Growth hormone is produced mainly as one nocturnal burst. Cortisol is produced in bursts throughout the night, reaching a daily maximum at c. 8 a.m.

Evoked responses/potentials: Averaged EEG tracings following stimulation of a particular sensory modality with 'background noise' eliminated has proven useful in the investigation of a number of neurological and psychiatric disorders. A graph of the typical contralateral response to tactile stimulation of

³⁵⁷ Sleep latency = lights out to first nREM stage I episode.

³⁵⁸ Sleep efficiency = time sleeping/time in bed X 100.

³⁵⁹ Therefore this cannot be depended on to make a diagnosis.

³⁶⁰ Phase advance of cortisol in depression is relatively small in magnitude and inconsistently reported. (Hajak & Popp, 2008, p. 82)

³⁶¹ Thalidomide and γ -hydroxybutyrate, both hypnotics, also increase slow-wave sleep. (Nishino ea, 1998)

³⁶² Anticholinergic/antimuscarinic drugs such as atropine, scopolamine, and TCAs can decrease REM sleep. (Wilson & Argyropoulos, 2005)

³⁶³ REM suppression by phenelzine is reversed by rapidly depleting tryptophan. (Landolt ea, 2003) This suggests that serotonin is involved.

³⁶⁴ But not trimipramine (Steiger, 2002), iprindole, or viloxazine, which have no significant effect on REM. (Le Bon, 2005)

³⁶⁵ Alcohol reduces sleep latency, REM and stage 4 sleep. It increases sleep fragmentation. 'Happy hour' or 'cocktail hour' drinking can cause initial insomnia.

³⁶⁶ Hence its use in treating REM sleep behaviour disorder.

an index finger would show an initial stimulus artefact followed in succession by a positive deflection P1, a negative deflection N1 and the P2 and N2 over a 60 millisecond (ms) period; amplitude is measured in μV . For example, Allen ea (1991) failed to find a significant difference in the lateralisation of tactile-evoked potentials when a stimulus was evoked to the index fingers of patients with schizophrenia and age- and sex-matched controls. P3 (P300) abnormalities (showing differences from controls) have been reported in schizophrenia, behavioural problems, (Iacono ea, 2002) memory disorders like Alzheimer's disease, attentional disorders, and, as a trait marker, in the offspring of alcoholics, (Polich ea, 1994) and in affective disorders (Hall ea, 2009); abnormalities may involve amplitude, latency or the positioning of the peak over the head. (Maurer, 1989) The P300 becomes prolonged with increasing age. (O'Donnell ea, 1995) Blackwood ea (1987) found the (auditory) P300 latency increased in schizophrenia and depression, returning to normal in the latter with recovery but remaining prolonged in the former and remaining uninfluenced by medication. The P50, a positive potential occurring 50 msec. after a stimulus, was examined by Siegel ea. (1984) Normal people show reduced amplitude in response to a second loud click presented half a second after a first loud click (heard through headphones), but many drug-naïve and medicated schizophrenic patients and about third to a half of their first-degree relatives fail to demonstrate this reduction, i.e. they fail to habituate.

Brain electrical activity mapping (BEAM) is a research tool wherein aspects of the EEG over the brain, such as frequency bands, are averaged by digital computer with the production of coloured areas representing levels of activity. (Duffy ea, 1979) BEAM offers a sensitive physiological measure of psychotropic drug effects. To a large extent, BEAM has been superseded by other neuroimaging techniques. An evoked potential is a time-locked average of the EEG in response to a specific sensory, motor, or cognitive event.

*Eye-tracking studies*³⁶⁷

SPEMs are responsible for slower moving targets than are saccades (see next) and involve continuous movements with fovea fixed on the target; they require stimulus activation and are maintained by attention to the target.

The subject looks at a smoothly moving target, such as a pendulum or a moving spot. The direction of gaze is measured by reflecting infrared light from the pupil. Most normal people will track in a smooth, sinusoidal fashion. Excess jerkiness - a disrupted, jagged pattern - is found in most, but not all, schizophrenic subjects, in about 45% of their parents and siblings - who may not have overt illness, and in around 8% of the general population. According to Kathmann ea, (2003) over 80% of have abnormal smooth pursuit tracking with about one in three of their relatives having similar problems.

Saccades

These are fast, ballistic eye movements that bring the fovea centralis and the target together, e.g. when a person hears a sound and turns the eye quickly to its source. Saccades can be voluntarily executed. The eye may jump ahead of the target (*anticipatory saccades*) or, because of reduced *gain* (speed of eye v speed of target), the eye falls behind the target and uses a *catch-up saccade* to bring it back to the target.

Antisaccades

A subject is asked to fixate a central dot that steps at random to left or right. When the target steps into the periphery the subject is asked to look away from the target to the opposite side. It requires inhibition of the temptation to look to the side where one remembers the target to be: when one must inhibit the reflex to look toward a light (*prosaccade*) and instead consciously look in the opposite direction (*antisaccade*), schizophrenic subjects have great difficulty not turning their eyes to the light. (Ford ea, 2004) There are reports (Serenio & Holzman, 1995) that antisaccade errors occur in schizophrenia and those schizotypal subjects, (O'Driscoll ea, 1998) with increased scores on the Perceptual Aberration Scale, (Chapman ea, 1978) tend to perseverate during this task.

Isotope brain scan

This technique is redundant.

*Cerebral blood flow (CBF)*³⁶⁸

³⁶⁷ Smooth pursuit eye movements: SPEMs.

³⁶⁸ CBF measurement using nitrous oxide was first described by Seymour Kety (1915-2000) and Carl Frederic Smith (1893-1988) in 1945.

CBF may be measured using Xenon 133 inhalation. Xenon is an inert gas that does not affect physiological or biochemical processes. Radioactivity can be measured using gamma detectors yielding a measure of regional CBF (rCBF). Because neuronal activity is directly correlated with blood flow, rCBF is a measure of local neuronal activity. However, this method tells us only about surface activity. Examination of deeper brain parts requires a technique such as PET (which allows a 3-dimensional quantification of brain physiological activity, either blood flow or receptor activity).

In normal healthy adults, the mean CBF is about 50 ml./100 g. of brain tissue/min. Values for white and gray matter are about 80 and 20 respectively. CBF tends to be higher frontally and to slowly decline with advancing age.

*Computerised tomographic (CT) Scans*³⁶⁹

The time needed for CT scanning has been reduced greatly (and continues to be) since its introduction. Spatial resolution of CT has also improved (< 1 mm). Whilst CT can image in the transaxial plane only, MRI can do so in transaxial, sagittal and coronal planes.



CT of brain

Voxel³⁷⁰ - volume element of CT scans: each brain slice is divided into a series of tiny cubes; a number representing the degree of the x-ray³⁷¹ beam (see Hounsfield number) can be assigned to each voxel, each then being assigned a shade of gray yielding a visual picture of brain function

Pixel (picture element) - the surface of a voxel and represents the average radiodensity of the entire underlying voxel

Hounsfield number – x-irradiation transmitted from a pixel is examined by a computer and its density is assigned a number; water has a 0 value, air = - 1000 units, and water = + 1000 units

CT may fail to demonstrate early infarcts, inflammation (cerebral abscess detection requires use of contrast), or very small lesions, especially if they are sited in brain stem or posterior fossa. The contrast dye used for CT has a high osmotic load that can cause acute renal failure in at-risk cases; patients must be well hydrated before receiving a contrast infusion. (Salloway ea, 2000) Seizures due to ionic contrast in CT affects 1 in 10,000 cases, more if the blood-brain barrier is significantly compromised.

Follow up of Swedish men who received radiation treatment for cutaneous haemangioma aged less than eighteen months found evidence of cognitive damage. (Hall ea, 2004) Because the doses received that led to adverse effects were equivalent to those from cranial CT, the authors warned of the need to re-evaluate the use of CT for children with minor head injuries.

³⁶⁹ The first prototype EMI head CT (low density x-rays) scanner was installed in Atkinson Morley's Hospital in London in 1972. Three years later a prototype whole-body scanner was installed at Northwick Park Hospital, Middlesex. When Eve Johnstone and co-workers conducted their CT work during the 1970s it was with one of two such machines in existence! Sir Godfrey (or Geoffrey) Hounsfield (1919-2004; Hounsfield, 1973) for which he received the Nobel Prize in 1979 invented the technique of CT. (Hemingway, 1991)

³⁷⁰ Voxel-based morphometry examines structural brain abnormalities using MRI: the data collected allows differences between groups in various brain areas to be identified.

³⁷¹ Radiation exposure with CT was said to be of the same order as a skull or chest X-ray making repetition problematic. However, there is increasing concern that the (over-) use of CT (e.g. in the private sector) may be causing cancer. (Kmietowicz, 2007) A typical scan is associated with a risk of 1 in 2000 of lifetime fatal cancer (natural risk = 1 in 4). (Kmietowicz, 2008)

Prospective studies in Alzheimer's disease patients have shown a worse prognosis in those with low attenuation density in the parietal lobes. One-quarter of schizophrenic patients show early signs which unrelated to inpatient care or medication; in two-thirds of these there is non-specific enlargement of the third and lateral ventricles; more localised lesions, such as aqueductal stenosis or septal cavities are also reported. A link between ventricular enlargement in more advanced schizophrenia and perinatal intraventricular haemorrhage has been suggested. (Lewis, 1986) reversible cerebral ventricular enlargement has been reported in both alcoholism (Carlen et al, 1978) and anorexia nervosa. (Heinz et al, 1977) Normal brain tissue shows as gray, CSF³⁷² as black, and white matter or the sagittal sinus and calcified pineal gland³⁷³ as white. CSF is also found in cerebral infarcts, chronic subdural haematomas and in brain oedema around tumours causing them to be darker than normal brain. *Hydrocephalus ex vacuo* infers an increased ventricular-brain ratio (VBR), e.g. in some cases of chronic schizophrenia. Some chronic cases of schizophrenic also lack the normal greater convolutions of the cortex over the dominant versus the non-dominant hemispheres, a finding that is not correlated with age, therapy, or electroconvulsive therapy (ECT). The normal elderly, even if highly intelligent, can have marked cerebral atrophy. The contents of a subdural haematoma are very dense at first, then become less dense³⁷⁴, and eventually are isodense with adjacent brain³⁷⁵.

Indications for CT

(a) *Psychiatric*³⁷⁶ (Renshaw & Rauch, 1999)

First episode of psychosis (Gewirtz, 1994)

Idiopathic confusion

Dementia

New psychiatric syndromes in > over-50s

Focal signs

History of head injury or seizures

(b) *Neurological*

Acute bleed (<1-3 days old)³⁷⁷

Acute injury

(c) *Patients with headache* (Peatfield, 1989)

Possible subarachnoid haemorrhage

Progressive increase in frequency/severity

Focal signs

Seizure (any type)

Vomiting

Endocrine dysfunction

Neurofibromatosis (including a family history of same)

Known malignancy elsewhere

*Positron emission tomography (PET) Scans*³⁷⁸

³⁷² Radiolucent – attenuates the x-ray beam the least.

³⁷³ Or other calcification or tumours, being radiodense – attenuates most, therefore appears lightest.

³⁷⁴ Due to haemolysis.

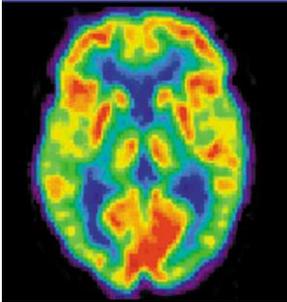
³⁷⁵ May be missed without contrast.

³⁷⁶ Great variation in diagnostic yield and type of referred patient in published studies make exact guidelines somewhat ephemeral.

³⁷⁷ Intracerebral bleeding becomes isodense with brain tissue by about the tenth day. **Diffusion weighted imaging** (DWI MRI) may oust CT from this indication. Diffusion weighted imaging detects random movement of tissue water and quantifies such movement using an *average apparent diffusion coefficient* which is then mapped onto the brain. Intracellular oedema (e.g. due to reduced blood supply) causes a reduction in this coefficient whereas diminished tissue integrity increases coefficient values. **MRI gradient echo sequences** picks up signals from paramagnetic material (e.g. iron) and so can detect haemosiderin, a residue of cerebral haemorrhage. One in twenty normal adults will have evidence of small parenchymal haemorrhages, although some haemosiderin deposits are removed over time.

³⁷⁸ PET ('PETT') was initiated by Michel Ter-Pogossian (1925-1996) of St Louis at a radiology meeting in 1974. The first PET scanner in the Republic of Ireland was housed at the Blackrock Clinic in Dublin. **Positron**: A positively charged particle with the same mass as an electron. If an isotope such as ¹⁵O₂ has more protons than neutrons it will emit positrons to achieve stability. The

PET scans inform us about cerebral metabolic activity. Energy is detected in the form of positrons produced during metabolism of substances such as fluorine-18-labelled fluorodeoxyglucose (FDG). FDG is metabolised just like glucose. Therefore, an increased positron³⁷⁹ emission rate indicates an increased metabolic rate and increased glucose utilisation. FDG has to be produced in a cyclotron. Radiation comes from the brain in PET scanning, but is passed through the brain in CT scanning. The very short half-life of the tracer allows collection of many images, separated by about 10 minute intervals, within a single session.(Liddle, 2000)



PET brain scan

Techniques have been used to highlight functions of different brain regions, the neurotransmitter function in disease, and to delineate dysfunctional brain areas.(Frackowiak & Jones, 1989; Dolan, 1989) Studies provide *in vivo* evidence for dopamine-2 (D2) receptor blockade by antipsychotic drugs,(Waddington, 1989) particularly strong in the case of typical agents. Schizophrenic patients with tardive dyskinesia (Fr *tardif*, late; *dyskinesia* [Gk. *dys*, bad; *kinēsis*, movement] simply means an abnormal movement and covers everything from tics and myoclonus to tremor, dystonia and chorea) may have increased metabolism in the basal ganglia with the opposite being found in Parkinson's disease. Mazziotta *et al.*,(1987) in a controlled study of Huntington's disease, reported a marked decrease in glucose metabolism in the caudate nuclei of both symptomatic and asymptomatic at-risk subjects. The reduced cerebral blood flow in Alzheimer's disease in posterior temporoparietal regions seen with SPECT shows as reduced glucose utilisation with PET. Multi-infarct dementia is characterised by patchy reductions in cerebral blood flow and metabolism,(Kumar, 1993) and fairly distinctive patterns are found in Pick's disease and Parkinson's disease with dementia. Major depression in the elderly is associated with reductions in whole brain glucose metabolic rates comparable in magnitude to those found in Alzheimer's disease.(Kumar, 1993) Areas of increased cerebral blood flow have been demonstrated in the hippocampal regions in patients with panic attacks.

*Single photon emission computerised tomography (SPECT or SPET)*³⁸⁰

While SPECT is mainly employed for measuring regional cerebral blood flow³⁸¹ (rCBF), PET measures rCBF, metabolic function, and neuroreceptor density. In SPECT the isotopes are single photon emitters whereas in PET they are positron emitters. Unlike PET, SPECT does not require an on-site cyclotron. Radio chemicals that emit a single photon or γ (gamma) ray, such as ¹²³I, are employed; the isotopes used in SPECT have a longer half-life than those used in PET. The latter fact makes it difficult to do multiple pictures at one sitting because one has to subtract residual radioactivity from any previous scan; also, high radiation exposure limits one to 2-3 scans/person/year.(Liddle, 2000) The resolution of PET is superior to that of SPECT, but SPECT imaging agents have greater half-lives than those used with PET, allowing a

positrons encounter (negatively charged) electrons causing mutual annihilation with simultaneous production of 2 photons (γ rays) of equal energy, but emitted in opposite directions. A scanner detects the photons and a computer reconstructs an image. While two photons are emitted with PET, only one is emitted with SPECT. Both PET and SPECT carry risks of radiation, disallowing repeated scanning.

³⁷⁹ A positively charged electron.

³⁸⁰ B. Leonard Holman (b. 1941) and Thomas C. Hill (b. 1945) of Boston introduced SPECT to neurology and psychiatry in 1984.

³⁸¹ Unlike PET, SPECT does not give an absolute value for rCBF. SPECT results were expressed as radioactive counts in each region of interest compared with a reference area (e.g. whole brain or cerebellum). However, the region of interest methodology has given way to various voxel-based techniques (e.g. *statistical parametric mapping* or SPM) in which voxel by voxel comparisons across the complete brain are used with the aim of finding patient-control clusters of disparity.

more prolonged and detailed neurochemistry study than is possible with PET.(Weinberger, 1993) For both SPECT and PET studies, an MRI or CT scan can be performed initially, with later superimposition of the PET or SPECT image: this allows for a more accurate anatomical location of functional data. Using the blood-flow marker hexamethylpropyleneamine (HMPAO) allows patterns of regional cerebral blood flow to be measured *in vivo*.

Up to 80% of Alzheimer patients show reduced blood flow (and glucose metabolism) in the cortex of posterior temporoparietal regions; there is relative sparing of primary sensory areas and subcortical regions.(Kumar, 1993) SPECT findings suggest a continuum between age-associated memory impairment and Alzheimer's disease.(Besson, 1998) Depression is associated with cerebral blood flow and/or metabolic changes in the fronto-temporal cortex and caudate nucleus.(Cummings, 1993) Lesser ea(1994) compared physically healthy depressives over 50 years of age with normal controls: rCBF was lower in older, medication-free depressives, involved the orbital frontal and anterior temporal regions, and was lowest in the right hemisphere. During tasks that activate the frontal lobes, patients with schizophrenia, unlike controls, fail to increase blood flow to the frontal cortex.(Weinberg ea, 1986; Lewis ea, 1992; Berman ea, 1993) In one study,(Marshall ea, 1993) 10 epileptic patients, half with schizophrenia-like psychoses, underwent SPECT; the psychotic patients had diminished rCBF in the left medial temporal region.

*Magnetic resonance imaging (MRI) or nuclear magnetic resonance (NMR)*³⁸²

MRI provides a high degree of contrast between gray and white matter and, unlike CT scan, is not impeded by bone. Paramagnetic contrast medium (e.g. gadolinium-DTPA: such media cross the blood-brain barrier and change tissue relaxation time; they are usually well tolerated) may distinguish between oedema and neoplasm (it is difficult to distinguish the two with MRI). MRI does not show calcification. It is useful for delineating problems in the posterior fossa, the cranio-cervical junction, and the neural canal.

MRI (e.g. Scheele ea, 1997)

Nuclei in a constant magnetic field can be made to resonate by applying an oscillating magnetic field in the radiofrequency range

As the resonance decays to zero the radiofrequency radiation emitted by the nuclei can be detected (the basis of the MRI signal)

Can measure time taken for nuclei to return to their original equilibrium

The proton relaxation parameters, T1 (spin-lattice: represents relaxation along *longitudinal* axis) and T2 (spin-spin: relaxation along *transverse* plane) are sensitive to pathophysiological change, particularly shifts in water distribution

Each tissue has specific T1 and T2 values

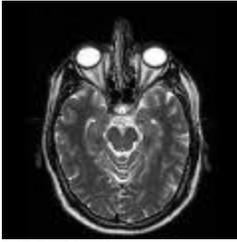
On T1 images, cerebrospinal fluid and abnormal areas are relatively dark, and vice versa on T2 images

T2 weighted sequences – good for showing abnormal tissue, for showing structure

T1 weighted images – good for showing structure

MRI may interfere with cardiac pacemakers and shift or heat prostheses, aneurysm clips or shrapnel; metal plates in the skull and cochlear implants are also a problem. Ferromagnetic material in a tooth filling can cause artefacts. With use of adjustable valves with subcutaneous magnetically controlled mechanisms to allow clinical manipulation of CSF drainage in normal pressure hydrocephalus the patient must avoid magnets, including MRI scanners. Loose metallic objects (such as a paper or hair clip) can become a lethal weapon when close to an MRI machine!

³⁸² An early discussion is provided by Steiner.(1987) The phenomenon of magnetic resonance was described in 1946, gaining the nobel prize for physics for Felix Bloch and Edward Mills Purcell in 1952. The first clinical demonstration of intracranial pathology using MRI was reported by Hawkes ea.(1980) Peter Mansfield of Nottingham and Paul Lauterbur of Illinois shared the nobel prize in physiology or medicine in 2003 for their work in developing MRI.(Mayor, 2003)



MRI of brain

Chick embryos are vulnerable to the increase in temperature associated with MRI suggesting that this procedure should only be used in the first trimester of pregnancy unless very necessary.(Godlee, 1991) Because MRI takes much longer (classically 5-60 mins.) than CT (classically 1-5 mins.) there may be difficulties with phobic or disturbed subjects; however, new, fast MRI techniques may allow a full brain image in seconds.(Liddle, 2000)³⁸³ Also, the clinician must inform the radiologist of what is being sought in order that the latter can produce the type of image most likely to show it up.

One American MRI study (Rauch & Renshaw, 1995) of psychiatric patients (N = 6,200) revealed only 1.6% with unexpected and potentially treatable findings. Brain responses were recorded by Mander ea, (1987) in 14 patients with major depression during a course of ECT. T1 relaxation time rose immediately after the fit, reaching a maximum 4-6 hours later, T1 values then returning to baseline. No long-term increase occurred over the course of treatment. Such results are consistent with an extensive but temporary breakdown of the blood-brain barrier during ECT. MRI (especially fluid-attenuated inversion-recovery: FLAIR³⁸⁴) demonstrates demyelinated plaques in multiple sclerosis, a task beyond CT. Psychosis in multiple sclerosis patients may be associated with a high total lesion score on MRI, and especially with lesions around the temporal horn.(Feinstein ea, 1992) Gaffney ea (1987) reported enlargement of the fourth ventricle in autism. According to Miller ea,(1991) patients with a first psychotic episode after 45 years of age have more MRI abnormalities, are more likely to have large white matter lesions or metabolic disorder, and do more poorly on neuropsychological tests, especially those evaluating frontal lobe and memory abilities, than healthy age-matched controls. Interestingly, in a very small study of patients with cerebral trauma,(Buckley ea, 1993) those with an illness resembling schizophrenia, but not those with a schizoaffective-like disorder, had left temporal lobe abnormalities. MRI has demonstrated reduced amygdaloid and hippocampal volumes in schizophrenia.(Carpenter & Buchanan, 1994) Stefanis ea (1999) found that exposure to obstetric hazards could be associated with small hippocampus volume; animal research has demonstrated that lesioning of neonatal ventral hippocampus reduces spine density in prefrontal cortex and accumbens nuclei and such rats, when mature, over react to amphetamine. In the Rangel-Guerra ea (1983) study of bipolar affective disorder patients, the latter had longer brain proton T1 relaxation times that normalised after lithium treatment, whereas lithium had no effect on this parameter in normal control subjects.

Knauth ea (1997) demonstrated multiple brain lesions in sport divers in association with a large patent foramen ovale³⁸⁵ that might be explained by paradoxical arterial gas embolism. Subdural haematoma in T1-weighted images initially has an intensity between CSF and cerebral cortex; the signal increases thereafter; and finally it may be isointense with cortex.

Diffusion tensor imaging (DTI)

This MRI-derived technique examines the axes along which water diffuses. It provides information on the directional orientation of white matter tracts and informs us of their structural integrity.(Conturo ea, 1999) It can be used to detect disorders involving partial or complete disconnection between regions of the brain, or to detect demyelination. High values of fractional anisotropy³⁸⁶ indicate intact healthy neurones.

³⁸³ The MRI signal is detected by a receiver/detector coil. Newer coils allow parallel imaging. SENSE (sensitivity encoding) and SMASH (simultaneous acquisition of spatial harmonics) shorten image acquisition time.

³⁸⁴ FLAIR produces heavily weighted T2 images. CSF signal is suppressed and contrast between grey and white matter is reduced. The result is that lesions at the CSF-parenchyma junction are easier to see.

³⁸⁵ One-quarter of sport divers have a patent foramen ovale.

³⁸⁶ Anisotropic = directional. Tractography involves calculating fractional anisotropy, i.e. the degree of directional preference of bundles of fibres in a given voxel.

Fractional anisotropy results range from 0 to 1, higher values indicating greater directionality (more coherent fibre orientation) and lower values reflecting poor white matter integrity or disruption.

DTI applications – some examples

Schizophrenia

Reduced white matter tract integrity in left uncinate and arcuate fasciculi (Burns et al, 2003)
 White matter microstructural disruption (Andreone et al, 2007; Skelly et al, 2008; Cheung et al, 2008)
 Reduced interhemispheric connectivity between frontal areas via corpus callosum (Kubicki et al, 2008)
 No differences in white matter abnormalities between schizophrenia and bipolar disorder (Sussmann et al, 2009)

Hallucinations

During inner speech, alterations in white matter tracts in patients with frequent hallucinations lead to co-activation in regions related to the processing of external sounds (Hubl et al, 2004)

Bipolar affective disorder

Decreased fractional anisotropy in superior-frontal white matter tracts in bipolar adolescents (Adler et al, 2006)
 Fronto-temporal white matter abnormalities (Bruno et al, 2008)
 Smaller anterior cingulum (Wang et al, 2008)

Major depression

Abnormalities of brain white matter in treatment-naïve young adult major depressives (Ma et al, 2007)

Geriatric depression

Lower fractional anisotropy in distributed cerebral networks associated with poor response to escitalopram (Alexopoulos et al, 2008)

Geriatric cognition

In dementia-free elders, white matter integrity is associated with cognitive function even when white matter appears normal on MRI (Vernooij et al, 2009)

Magnetisation transfer imaging (MTI)

MTI allows visualisation of protons that are bound tightly to macromolecular structures like myelin and cellular membranes in white matter. The normal brain signal, expressed as the magnetisation transfer ratio (MTR), is more or less the same in all voxels. MTI has revealed abnormalities in frontotemporal areas in schizophrenia (Foong et al, 2001). Magnetisation transfer increases the contrast between liquids and solids and can visualise blood vessels when employed in magnetic resonance angiography.

Magnetic resonance angiography (MRA)

MRI variables can be made sensitive to motion to allow for angiography of small arterial branches or visualisation of venous outflow without the use of contrast agents (Scheele et al, 1997)³⁸⁷

Event-related optical signal (EROS)

In this technique, near-infrared light is beamed through the skull into cortex (Gratton & Fabiani, 1998). This light is deflected, providing cerebral haemodynamic information ('slow signal' which tracks changes over seconds) and data on neuronal shape alterations due to neuronal firing ('fast signal' measured in milliseconds). By controlling the position of light source and detector and by extremely fast recording (in milliseconds) one can get an idea of signal source and temporal change. Because of poor penetration of light, activation of deep brain structures are not detected.

Functional MRI (fMRI)

This fast (David et al, 1994) procedure does not require radioactive materials and permits measurement of neural activity with higher temporal resolution than SPECT or PET. It can be performed simultaneously with MRI. fMRI can carry out spatial resolution within the millimetre scale and can capture responses in brain occurring over a few seconds (including sensorimotor and cognitive activities, e.g. auditory hallucinations). It uses the brain's natural haemodynamic response to neural activity as an endogenous tracer. The commonest form is *blood oxygenation level dependent (BOLD) imaging*: this depends on the ratio of oxygenated to deoxygenated haemoglobin³⁸⁸. Tasks can be given to the subject to perform whilst brain activity is measured. BOLD fMRI measures an index of change in blood flow but cannot measure absolute resting/baseline blood flow³⁸⁹. The subject must tolerate scanner noise³⁹⁰ and close confinement

³⁸⁷ Thanks to the pioneering work of Charles Dumoulin during the 1980s.

³⁸⁸ Increased neuronal activity leads to increased local blood flow (*neurovascular coupling*) and a **decrease** in deoxyhaemoglobin because the increase in blood flow is greater than the power of the cells to consume oxygen. Oxygenated haemoglobin is slightly diamagnetic and causes weak disturbances in the local magnetic field. On the other hand, deoxyhaemoglobin is paramagnetic, aligns with an applied magnetic field, and increases the strength of the local magnetic field.

³⁸⁹ This may become possible with a magnetic resonance technique called *arterial spin labelling*.

³⁹⁰ A loud bumping noise caused by switching of the gradient coils.

within the magnetic bore, and the subject must not possess a magnetic implant. All that is required is upgraded software for standard MRI scanners.(Longworth ea, 1999) Artefacts mimicking changes in neuronal activity can be produced by movement of the patient.(Sheringham ea, 2002)

*Magnetic resonance spectroscopy (MRS)*³⁹¹

MRI goes beyond static visualisation of white and gray matter and enables measurement of cerebral blood flow and analysis of cerebral drug concentrations. While both SPECT and PET require the use of manufactured radioactive compounds, MRS utilises naturally occurring, nonradioactive nuclei. Natural emissions from atomic nuclei activated by magnetic fields are used to measure concentrations of molecules within the body. There are no 'pictures', just quantitative measurements, a display of the spectrum of certain chemicals. It has been used to study regional changes in GABA, to detect fluorine-containing drugs at receptor sites, and to image lithium in the brain.(Lock ea, 1990) N-acetyl aspartate³⁹² (NAA) is found mainly in neurones and can be measured by proton magnetic resonance spectroscopy.

Using this technique, Nasrallah ea (1994) found reduced NAA intensities in the right hippocampus/amygdala region of patients with schizophrenia, the left side being no different from normal controls; these findings led the authors to speculate that the right side might have less neurones or have biochemical alterations in NAA in schizophrenia. MRS findings suggest early abnormalities in the synthesis of membrane phospholipids in Alzheimer's disease but not in vascular dementia, which may prove helpful in differential diagnosis.(Besson, 1998)

*Transcranial magnetic stimulation (TMS)*³⁹³

TMS allows non-invasive induction of electrical currents in a restricted part of the cerebral cortex. When combined with electromyography (EMG), TMS of primary motor cortex can reveal changes in motor physiology evinced by experimental manipulations, as well as changes associated with psychiatric and neurological conditions. TMS can induce temporary, focal 'virtual lesions': this allows one to tell if a region of cortex identified by neuroimaging (e.g. PET) is essential for a particular cognitive task. The effects of relatively prolonged alterations in cortical excitability on a person's performance can be studied following use of repetitive TMS (rTMS). Combined PET and TMS is being used to assess neural connectivity: the effects of focal TMS is compared with changes in blood flow in another part of the brain. Assessment of local and distal blood flow changes with PEallows assessment of cortical excitability and connectivity respectfully. TMS can be combined with EEG in other research.(Paus, 2003)

Magnetoencephalography (MEG)

MEG measures magnetic fields.(O'Donohoe, 1989; Sato, 1990) When current flows down a conductor a magnetic field surrounds the conductor, an effect that can be detected in nerve fibres. This very small field can be measured at the scalp (a magnetically shielded room and very low temperatures for the loop are required). Fluid or tissues do not attenuate magnetic brain waves. The ability to detect deep brain discharges using this method may obviate the need for indwelling electrodes.

In one study,(Reite ea, 1997) controls demonstrated asymmetry in an auditory-evoked field component (100-msec. latency); male schizophrenics showed less asymmetry and female schizophrenics showed more asymmetry than controls.

Magnetic field tomography, derived from MEG data, allows construction of a picture of dynamic brain activity. Resolution and spatial accuracy declines as the further one moves from the cortex. It remains largely experimental.

Magnetic source imaging (MSI) combines structural MRI with magnetoencephalography and has been used, for example, in studies of cortical reorganisation following limb amputation.

Echoencephalography (ultrasound)

³⁹¹ **Main techniques of MRS:** (a) *Proton spectroscopy*: measures the metabolite N-acetylaspartate, a marker of neuronal damage that is diminished in both Alzheimer's and Creutzfeldt-Jacob diseases. (b) *Phosphorus spectroscopy*: a direct measurement, in vivo, of phospholipid metabolism; phosphomonoesters reflect rate of membrane phospholipid synthesis; phosphodiester reflect rate of degeneration of membrane phospholipids. **Principle behind MRS:** In a magnetic field each distinct nuclear species has a unique spin frequency known as a Larmor frequency. This frequency varies with the compound containing the element in question. Application of a radiofrequency pulse tuned to the frequency of the specific element yields a spectrum that is caused by the different compounds containing the specific element.

³⁹² **NAA signal** is almost exclusive to nerve cells. A decrease in signal likely means dysfunction of neurones. Choline-related metabolites contribute to the Cho peak on MRS. Brain injury is associated with a higher Cho peak. Cr (creatine) peak is generally immune to the effects of brain damage. NAA and Cho activity are reflected respectively in NAA/Cr and Cho/Cr ratios.

³⁹³ The therapeutic use of TMS is discussed elsewhere.

This procedure has a high yield of false positive and negative results and has been superseded in studies of schizophrenia by CT and MRI. Directional Doppler ultrasonography may show narrowed blood vessels. Prenatal ultrasonography at 19-23 weeks gestation found a non-significant trend towards increased lateral ventricular width in offspring of mothers with psychosis.(Clarke ea, 2007)

Radioisotope (radionuclide) scan

An isotope is given by IV injection and is taken up by vascular tissue (tumours, infarcts). This procedure has become uncommon since CT was introduced.

Cognitive subtraction paradigm

An image of neural activity (be it blood flow or electrical activity) is taken before (control state) and during (task state) a task and the difference (subtraction) shows what brain parts are used for that task. In practice averages across intra- and interindividual repeated task performance are used in order to control for 'noise'.

Sleep disorders

Sleep disorders in children, although distressing at the time, are mostly developmental: they grow out of them. Behavioural techniques and education are often sufficient intervention. Clues to the need for further investigation are very frequent occurrence, onset in or persistence into late childhood, appearance after a traumatic event, and other evidence of psychological disturbance.(Stores, 1990)

Insomnia: Insomnia is the complaint that a person finds it difficult to fall asleep, stay asleep, or achieve good quality sleep. Chronic insomnia affects 10-15% of the population, and is more common in women and in older people.

Insomnia classifications

Primary ('psychophysiological' because psychological and physical factors operate)

Secondary (e.g. pain³⁹⁴)

OR

Transient e.g. on a long voyage or during a period of emotional distress

Prolonged e.g. in hypomania or other psychiatric illness

OR

True

Pseudo – see sleep-state misrepresentation below

OR

Early (onset, initial)

Middle (maintenance)

Late (early morning wakening)

Prolonged sleep deprivation may impair intellectual performance and disturb mood (During the 1950s, schizophrenic patients were kept awake because analysts considered dreaming as psychotogenic! Wehr, 1990), even to the point of inducing mania.(Wehr, 1991) Loss of sleep on occasional nights is of little medical significance. Insomnia is usually secondary (e.g. depression or anxiety) if accompanied by diurnal symptoms. Alcohol taken in excess can itself cause insomnia and sleep disturbance may persist for weeks after cessation of heavy alcohol intake. It should be recalled that many people with 'insomnia' ('pseudoinomnia' or 'sleep-state misperception') probably do have enough sleep, e.g. 50% of 'insomniacs' have no abnormality on polysomnography.(Kelsey ea, 2006, p. 263)

Although estimates vary greatly, insomnia costs around \$100 bn annually in the USA.(Neylan ea, 2003, p. 978)

Treatment depends on the cause. Stimulating drugs, such as tranylcypromine, should not be taken later than noon. Buspirone³⁹⁵ may increase wakefulness.(Manfredi ea, 1991) Drugs should be employed for brief

³⁹⁴ Also medication (e.g. phenylephrine, corticosteroids, MAOIs, SSRIs), illegal drugs (e.g. amphetamines), tobacco, drug withdrawal (e.g. alcohol), orthopaedic or rheumatological disorders, COPD, asthma, sinusitis, peptic ulcer, gastro-oesophageal reflux, peripheral vascular disease (cramps in legs), paroxysmal nocturnal dyspnoea, congestive heart failure (orthopnoea), dementia, menopause (hot flushes), diabetes (e.g. polyuria), Parkinson's disease, dementia, etc.

periods only where possible and dose should be tapered when the drug is used regularly for more than a couple of weeks. Ultra-short acting agents may produce daytime anxiety but are less likely than longer acting agents to produce daytime drowsiness.

Ramelteon, useful for chronic insomnia, is an MT1 and MT2 melatonin receptor selective agonist and hypnotic that may lack abuse potential. Ramelteon reduces sleep latency with no significant rebound insomnia or abstinence syndrome. It appears to possess safe motor and cognitive profiles. Psychological approaches include education (e.g. sleep hygiene measures) and behavioural and cognitive techniques. CBT where available, is effective for insomnia where people associate the bedroom with arousal and upset (rather than with sleep and sex). Fear of bedtime and catastrophising about sleep loss (negative automatic thoughts) need to be confronted. CBT includes stimulus control (only stay in bed when asleep; write anything that is on one's mind down during the evening, e.g. what needs to be done next day; paradoxical intention – deliberately trying to stay awake may lead to sleep), and relaxation³⁹⁶ (muscle relaxation, warm bath, meditation, autogenic training). One should rise at the same time every day. The patient should confine time in bed to time spent asleep so as to increase sleep efficiency ($[\text{time asleep}/\text{time in bed}] \times 100 = \text{sleep efficiency}$).

Lack of sleep in young doctors may be associated with a significant slowing in cognitive processing, a decline in reaction times, and deleterious changes in mood. (Orton & Gruzelier, 1989) Sleep deprivation, popular in the 1970s, led to transient improvement in depression. Increased DA release in the basal ganglia is one suggested effect of sleep deprivation. Sleep advance involves bringing the sleep-wake cycle forward by about 5 hours; again, improvement in depressed mood may not be maintained for any useful length of time. (Sovetre, ea, 1987) although there is some evidence of augmentation of this effect by lithium. (Grube & Hartwich, 1990) It has been suggested that increased cingulate activity prior to sleep deprivation may herald a useful antidepressant response to this procedure. (Ebert ea, 1994) There is some evidence that the old adage 'early to bed and early to rise' (phase-advance) may, especially if combined with appropriate medication, may have longer-lasting (a week) ameliorative effects on depressed mood than has sleep deprivation (a day). Improved mood after one night's sleep deprivation favours depressive pseudodementia over organic dementia³⁹⁷; the latter is likely to worsen under these circumstances. (Leibenluft & Wehr, 1992) Lithium increases theta (slow) activity³⁹⁸ whereas benzodiazepines increase beta (fast) activity and depression is associated with reduced delta (very slow) activity.

Sleep deprivation effects (Uhde & Singareddy, 2002)

Major depression	improved ³⁹⁹
Panic disorder	worse
OCD	no consistent change

Various psychostimulants can cause insomnia.

High altitude insomnia

In severe cases it occurs as part of acute mountain sickness (AMS)

Possible mechanism: fluid imbalance secondary to hypoxia

Short half-life hypnotics (e.g. zolpidem) may relieve the insomnia

Acetazolamide at 250 mgs. b.i.d. prevents or ameliorates symptoms of AMS (Roberts, 1994)

³⁹⁵ Buspar was withdrawn, December 2009.

³⁹⁶ Imagery and muscle relaxation are learned during daytime and applied in bed.

³⁹⁷ People with dementia or brain damage may have irregular periods of sleep throughout the day. The total time spent asleep during 24 hours may be normal. It may be a voluntary practice in some people. This *irregular sleep-wake rhythm* is managed by engaging the patient in captivating diurnal activities, morning light exposure, and retiring at the same time each day.

³⁹⁸ Lithium is associated with a high frequency of paroxysmal EEG changes, even in subjects with therapeutic serum levels and no gross signs of toxicity.

³⁹⁹ Deprivation of sleep (total or second half of night only) quickly improves symptoms of depression in many patients but the effect is lost with a night's sleep. However, when used with lithium or antidepressant drugs, such deprivation may produce more sustained effects.

The elderly have very little deep (stage 4) sleep, waken often at night, have a slight diminution in total REM sleep and in total sleep duration, as well as an increase in sleep latency. In fact, the typical insomniac is the thin, old, 'neurotic' woman who smokes a lot. Many factors may aggravate sleep problems in the elderly, such as pain, bladder or bowel problems, anxiety, depression, and dementia. The morning drowsiness of the sleep apnoea sufferer and the syndrome of 'restless legs' are less common causes of sleeplessness. Geriatric in-patients suffer from the high levels of background noise to be found in our hospitals. The doctor himself may cause insomnia with thiazide diuretics or MAOIs⁴⁰⁰, calcium blockers, phenytoin, anovulants, stimulating TCAs, alpha-methyl dopa, propranolol, thyroid hormone, caffeine, antimetabolites, some decongestants, bronchodilators, and corticosteroids or ACTH, or stopping antihistamines. The latter are useful as short-term sedatives but basically ineffective as anxiolytics. Elderly insomniacs should be encouraged to stop smoking⁴⁰¹, temper their intake of alcohol, avoid caffeine, take exercise, develop regular hours of sleeping and waking and, when necessary, use one of the hypnotics with a relatively short half-life. Alcohol is an often ineffective hypnotic because of dehydration, micturition and early morning rebound. Non-pharmacological measures such as sleep hygiene (Sateia & Nowell, 2004) or hot milk drinks should be tried before drugs. Chlormethiazole causes little in the way of hangover, can lead to troublesome sneezing, and there is an unpleasant taste from the liquid preparation. Chloral betaine can cause dyspepsia. One should remember that the half-lives of BZDs vary from one preparation to another, from flurazepam (long) to triazolam (very short). Use of a BZD of long half-life may cause confusion, incontinence, irritability, falls (Evans, 2003; Glass ea, 2005) and immobility.⁴⁰² Ideally, a hypnotic drug should be prescribed in the lowest dose possible, be eliminated quickly, used intermittently, the course should be short (max. 1 month), the patient should be counselled at the commencement of therapy, and alcohol should be avoided. CBT may be effective for insomnia. (Sivertsen & Nordhus, 2007) *Valerian officinalis* (Valerian) contains many chemicals (valepotriates). One such constituent, valerenic acid, has GABA-ergic properties and is sedative and anticonvulsant. Headache, blurred vision, gastrointestinal symptoms, dystonia, hangover and potentiation of other CNS depressants have been reported. It should be avoided in the presence of hepatic dysfunction. Some sleep disorders in *infants and young children* are briefly discussed here. Some young children will fall asleep in their mother's arms or in the parental bed. When asleep they are moved to the cot where they wake and refuse to sleep until taken back into mother's arms or the parental bed, a practice that reinforces the practice. This phenomenon is called *sleep onset association disorder*. The parent should settle the child in its crib/cot without removing it to a different setting and parental intervention should be gradually delayed throughout the night. As a bridging measure, a parent may need to spend some (decreasing) time sleeping in the child's room. Parents have to tolerate the child's crying and to intervene after longer periods of time, so-called 'controlled crying'. Antihistamines (e.g. trimeprazine) should only be employed for a short time and only to help parents through a period of extreme stress. Sleep hygiene measures in this age group include maintaining the same bedtime routine (short, pleasant, calm, predictable, with decreasing input from parent over time) and timing: give (non-stimulating) food/(non-excessive) drinks at least an hour before bedtime to obviate hunger; the room should be quiet and cool; do not play or feed the child in the sleeping environment; wake child at same time every day; and allow naps only as suits the age of the child. When parents do not insist on specific bedtimes the child will employ strategies to delay going to bed (*limit-setting sleep disorder*). A firm, non-hostile approach is needed that takes into account any fears the child may have (e.g. showing the child that there are no 'monsters' under the bed). The parent may spend a little time in the bedroom to sooth the child. Although sedatives are not indicated, medications are sometimes prescribed in practice.

Some sleep-related problems

Bruxism: involuntary, forceful grinding or clenching of the teeth during any stage of sleep; particularly likely in stages 1 and 2; diurnal bruxism is associated with dopamine blockade and recreational drug use

⁴⁰⁰ Give either early in the day.

⁴⁰¹ Smokers sleep less than non-smokers and nicotine withdrawal may cause drowsiness or arousal; nicotine itself causes initial insomnia and nicotine patches can cause vivid dreams/nightmares.

⁴⁰² However, whilst hypnotic/anxiolytic and antidepressant drugs are important predictors of falling, one study of elderly women found that chronic physical diseases (circulatory, COPD, depression, arthritis) were even more predictive. (Lawlor ea, 2003)

(especially ecstasy); anxiety, alcohol, malocclusion, venlafaxine (a 5-HT/noradrenaline reuptake inhibitor; responds to gabapentin), and SSRIs (treat by reducing dose or giving buspirone⁴⁰³; Romanelli ea, 1996; Wise, 2001) such as paroxetine, fluoxetine, sertraline, and citalopram (Cipramil),(Ellison & Stanziani, 1993) are associated factors in nocturnal cases; 15% of normal people may have bruxism; the noise may waken everyone except the patient; longstay inpatients with schizophrenia⁴⁰⁴ may have an excess of bruxism, severe dental wear, and temporomandibular problems.(Gurbuz ea, 2009)

Daytime drowsiness: There is a circadian tendency to feel mildly sleepy in the mid-afternoon. Causes of excessive daytime sleepiness include chronic sleep disorders such as obstructive sleep apnoea, narcolepsy, idiopathic hypersomnia⁴⁰⁵, insomnia, and periodic limb-movement disorder; depression; tertiary tricyclics such as imipramine⁴⁰⁶ or dothiepin (dosulepin) which cause hangover; BZDs and other sedatives; SSRIs (which can disrupt sleep – although paroxetine is more sedative); voluntary reduced sleep time (*insufficient sleep syndrome*), especially likely in young adults; and sleep reversal, e.g. psychiatric disorder, delayed sleep phase syndrome, coming off shift work, and travel. All of these may lead to accidents.(Leger, 1994; Hublin ea, 1996; Pilcher & Huffcutt AI, 1996; Terán-Santos ea, 1999) All dopamine agonists, to a variable degree, may be associated with somnolence. When somnolence occurs suddenly it may lead to accidents. Such adverse effects have most commonly been reported with ropinirole⁴⁰⁷, pramipexole⁴⁰⁸, and, less certainly, carbergoline.(Irish Medicines Board, 2002) The Multiple Sleep Latency Test (MSLT) allows a patient the chance to nod off in a dark room for 5 twenty-minute periods in 2 hour intervals across the subject's usual period of wakefulness: the average latency to sleep onset (measured with polysomnography) is a measure of the tendency to fall asleep.(Carskadon ea, 1986) Some centres test urine for drugs before MSLT in order to rule of people that are simply looking for stimulant drugs.

*Fatal familial insomnia*⁴⁰⁹: a very rare, untreatable prion⁴¹⁰-induced (caused by a mutation in the PRNP gene; Mastrianni ea, 1999) spongiform encephalopathy, is characterised by progressive insomnia (the usual presenting feature⁴¹¹), dysautonomia, ataxia, late diffuse EEG slowing, and thalamic nuclear, olivary and, to a lesser extent, cerebellar atrophy. Protease-resistant PrP (PrP 27-30) can be weakly demonstrated by immunoblotting; usually this is confined to the thalamus and temporal lobe. The average age of onset is 48 years and it lasts for about 18 months before death (range: 7-33 months) which is preceded by motor disturbance, wasting, and coma. Most, but not all, cases are familial with an autosomal dominant pattern.

Insomnia: (see text) difficulty initiating or maintaining sleep, or poor sleep quality; may be due to poor sleep hygiene⁴¹² (too much noise, caffeine [e.g. in chocolate], worry, heat, stuffy room, uncomfortable bed, etc; Espie, 1993), psychiatric disorders (e.g. anxiety disorder, agitated depression, etc), physical illness (, pain, age (need less sleep with age), jet lag, shift work, etc.

Jactatio capitis nocturna: Usually occurring at the start of sleep in infants, there is rhythmic head rocking (or banging) or, less commonly whole body rocking. Management involves measures to prevent injury. Clonazepam is used for severe cases.

Kleine-Levin syndrome (recurrent hypersomnia): rare disorder described by Kleine, 1925, and Levin, 1929; mostly affects adolescent males; periods of excessive eating (if food is put in front of them), sleeping and sexual activity lasting days or weeks; patient remains rousable and wakes spontaneously to eat, go to the toilet, etc; irritability (aggression sometimes), confusion, depression, elation, and visual and auditory hallucinations may occur; malaise, anorexia, and headache may follow attacks; little or none of the attack is recalled; most patients have 7-8 attacks and are well thereafter, i.e. it often improves with maturation (duration of disease is about 4-8 years: Gadoth ea, 2001); may have hypothalamic origin (Thompson ea,

⁴⁰³ Buspar was withdrawn, December 2009.

⁴⁰⁴ A number of factors may be responsible: illness, medication, dental hygiene, and lifestyle.

⁴⁰⁵ Hypersomnia (tendency to fall asleep during the day) should be differentiated from fatigue.

⁴⁰⁶ Imipramine (Tofranil), withdrawn 2006.

⁴⁰⁷ Ropinirole, a selective dopamine receptor agonist used for treating Parkinson's disease, can cause confusion and hallucinations.

⁴⁰⁸ Pramipexole, a dopamine agonist, may cause sedation, nausea, and hallucinations but has a reduced tendency to cause dyskinesia. It has antidepressant properties (including in Parkinson's disease) and may induce mania.

⁴⁰⁹ AKA fatal progressive insomnia with dysautonomia or familial thalamic degeneration.

⁴¹⁰ **Prion:** most basic of infectious agents; a single protein molecule with no nucleic acid; can catalyse conformational change in PrP (an endogenous protein) leading to changes in structure and function (i.e. disease): endogenous PrP^c is converted to the protease-resistant isoform PrP^{res}.

⁴¹¹ After some months the patient cannot sleep at all but may experience episodic stupor and enact dreams. Whilst conscious cognition is unremarkable. Persistent insomnia occurs in the last 1 or 2 years before death.

⁴¹² Clock-watching worsens insomnia. Clocks should be hidden or faced away from the sleeper.

1985); may follow acute viral infection; the experience of hunger is variable; EEG sometimes shows mild, diffuse abnormality, e.g. excess delta activity; however, EEG characteristics of sleep are normal. Similar disorders have been described in association with pathology in the midbrain and diencephalon. The syndrome has been treated with psychostimulants, SSRIs, MAOIs, or lithium.

Nocturnal paroxysmal dystonia: During sleep, especially stage 2, the patient awakens and experiences violent, uncontrollable movements. Much sleep is lost as a result. Treatment involves taking low dose carbamazepine.

Oneiroid psychosis (Gk.: dream, *oneiros*): described by W Mayer-Gross in schizophrenia; the patient feels and behaves as if in a dream; perplexity and disorientation are likely; may experience ecstasy and rapidly shifting hallucinations; while giving most of attention to an unreal world the sufferer is remains aware of the real world, e.g. while believing that one is flying one avoids walking in front of traffic.

Pickwickian syndrome: obesity; apnoea; short (seconds) bouts of CO₂ retention; EEG shows waking pattern or first 2 phases of N-REM sleep; uncommon cause of sleep apnoea.

*REM-sleep behaviour disorder*⁴¹³: recognised as a distinct condition in 1986 although lesions near the locus coeruleus in animals were already known to cause non-atonic REM sleep; increased frequency among elderly and in males; 'act out' their dreams with eyes closed and non-responsiveness to the environment; nocturnal vocalisation and violent limb movements; loss of normal REM-related atonia; reported in association with narcolepsy and with SSRIs, TCAs, MAOIs, and venlafaxine; treat with clonazepam (Schenck ea, 1987), carbamazepine, or donepezil. (Neylan ea, 2003, p. 987) Other suggested treatments include clonidine, melatonin, and pramipexole. It may be the presenting symptom of multiple system atrophy. (Plazzi ea, 1997) Parkinson's disease patients may develop REM-sleep behaviour disorder, sleep attacks (narcoleptiform; occur especially in those with general sleepiness and in those taking dopamine agonist drugs), restless legs, periodic limb movements, and an abnormal sleep-wake cycle. (Schrage, 2005) REM-sleep behaviour disorder may precede dementia with Lewy bodies by years. (Ericksen & Tsuang, 2007, p. 477) Multiple system atrophy, dementia with Lewy bodies, and Parkinson's disease are synucleinopathies and may be associated with REM-sleep behaviour disorder. As pointed out by Pivik (2002) motor inhibition can vary in degree during REM sleep, so movement of the sort reported in REM-sleep behaviour disorder is not impossible.

Shift work: If a person who normally sleeps at night naps early in the day they will experience an excess of REM, but a nap later in the day is associated with much less REM. People can readjust from a 24-hour pattern to a 36-hour or 18-hour pattern over a month or so. Shifts that rotate are more disruptive than fixed shift patterns. Shift workers do not adjust, especially as they age (presentation is usually after a number of years of shift work or because jobs or lives are put at risk). The fact that night shift workers may unknowingly fall asleep more often than day workers has significant safety implications. (Akerstedt, 1995) The main complaints are feeling unrefreshed, feeling sleepy, unable to sleep when required, and poor work or driving performance. An excess of depression and of anxiety has been reported in shift workers who undergo regular changes in their sleep-wake cycles. (Gordon ea, 1986) A major problem is lack of catch-up sleep during days off because of social reasons. There is some evidence that shift work (including airline personnel) increases the risk for cancer⁴¹⁴, especially cancer of the breast. (Fritschi, 2009) Use of melatonin in shift workers does not seem to be effective. (Arendt ea, 1995; Neylan ea, 2003, p. 985) Modafinil taken an hour or less before a night shift or a short-acting hypnotic for daytime sleep may be necessary. Extreme cases may need to change jobs. It is advisable that employers move their workers to progressively later shifts (phase delay) than *vice versa*.

Sleep paralysis: can be normal or part of the narcoleptic syndrome; can occur at least once in one-quarter to one-half of the general population, but as a chronic condition it has a prevalence of only 3-6% (Pivik, 2002); cannot move for brief time on waking. Some sufferers are able to indicate their distress with mini-movements or noises. If sleep paralysis occurs on falling asleep it is designated as predormital, and if it occurs on awakening it is called postdormital. Predormital sleep paralysis is much more likely to be due to narcolepsy than is the same phenomenon occurring on waking. Some patients complain of a crushing

⁴¹³ False reliance on alleged REM-sleep behaviour disorder as a defence in court would not be expected to pass polysomnography testing.

⁴¹⁴ If this is true, what is the mechanism? Depressed production of melatonin by light, depressed immune function by corticosteroids, changes in cell/tissue proliferation control mechanisms, lifestyle (smoking, alcohol, and lack of exercise), and reduced vitamin D production are contenders.

sensation in the chest or of feeling some ominous presence nearby (hence the word ‘night-mare’ – a heavy woman crushing the body). Sleep paralysis is exacerbated by alcohol. African Americans have an elevated risk of sleep paralysis.(Friedman & Paradis, 2002) *Night nurse paralysis* refers to the classic onset of sleep paralysis in a person recovering from night duty (or an all-night party). Sleep paralysis may sometimes be aborted by a bed partner touching the paralysed muscles.

*Snoring*⁴¹⁵: snoring is due to supralaryngeal soft tissue vibration; weight should be reduced in cases of obesity, and tobacco smoking and alcohol should be avoided.(Rees, 1991; Parker ea, 2005) The sleeping partner may find ear plugs helpful. Lying on ones side instead of one’s back helps; tying an empty thread reel or tennis ball to the back of the pyjama top is a time-honoured ritual. Sleep nasendoscopy (flexible nasendoscope in sedated snorer) may indicate source of vibration. Nasal congestion, if present, should be attended to. Tonsillectomy, for large tonsils, may cure some cases. A mandibular advancement device may help in cases of a receding lower jaw (retrognathia). Uvulopalatopharyngoplasty and radiofrequency softening of the soft palate are specialist procedures. Thyroid dysfunction and sleep apnoea should be considered in the differential diagnosis.

Somniloquy (sleep-talking): common in children and adults; can occur in any sleep stage; usually difficult to decipher what is said; longer sessions concern daytime preoccupations; do not reveal dream content and most unlikely to reveal secrets, contrary to popular opinion; may sometimes be associated with somnambulism or night terrors.

Sundowning: onset or exacerbation of delirium during evening or night, with improvement or disappearance of delirium during the day; increases during winter months because of less available natural light.(Bliwise ea, 1989)

Jet lag (JL): The traveller who crosses a number of time zones finds that the circadian pacemaker tries to maintain the phase set to the time zone of departure. The symptoms of JL include tiredness, difficulty in initiating sleep and in awakening, mood disturbance, anxiety, poor concentration, and, in some cases, gastrointestinal upset. To compensate, some travellers use a short half-life hypnotic for a few nights after arrival at their destination. If travelling east it is advised that melatonin should be taken in the late afternoon for one day before the flight and for 4 days at local bedtime after the flight to achieve an advance phase shift. Phase delay occurs after travelling west if post-flight melatonin is taken for 4 days at local bedtime.(Arendt ea, 1995) However, controlled studies of melatonin therapy in JL are negative.(Neylan ea, 2003, p. 985; Buscemi ea, 2006) According to Leonard,(2003, p. 144) the 5-HT2 antagonist ritanserin may improve sleep quality in JL sufferers. Alcohol should be avoided on such journeys and the traveller should attempt to adopt the sleeping schedules of his/her destination.

Sleep apnoea: Most cases are undiagnosed (Ancoli-Israel ea, 1991) and may be mistaken for depression⁴¹⁶. It may affect about 25% of people over 65 years of age, the classic case being a fat man with a fat neck⁴¹⁷. Not all cases are obese, in which case there is excess fat in the nasopharynx or enlarged tonsils. There are recurring episodes of apnoea and hypopnoea during sleep.(West ea, 2009) Severe oxygen desaturation may develop which may cause serious ventricular arrhythmias⁴¹⁸. Most cases are due to intermittent obstruction of the upper airways but there is a central form due to intermittent failure of the central respiratory drive during sleep.⁴¹⁹ In the obstructive type the patient makes strong efforts to overcome the block, even to the point of *paradoxical breathing* when chest and abdomen move in opposite directions. In central cases there is no attempt to initiate thoraco-lumbar respiratory effort. Mixed apnoeas may be the commonest type – here a central apnoea precedes an obstructive apnoea. The chief symptoms of sleep apnoea are loud

⁴¹⁵ The uncommon condition of *cathathrenia* or **sleep-related groaning** occurs during inhalation whereas snoring occurs during exhalation. Cathathrenia occurs in the last hours of sleep, especially during REM or deep sleep, and does not appear to be due to stress. The partner may find it disturbing and might wish to wear ear plugs. There is limited evidence for the efficacy of CPAP (see sleep apnoea).

⁴¹⁶ Fatigue, hopelessness, and low libido are common to both conditions.(Ancoli-Israel ea, 1991)

⁴¹⁷ Craniofacial anomalies (e.g. micrognathia), Down’s syndrome, adenoidal/tonsillar hypertrophy, stroke, hypothyroidism, myotonic dystrophy, COPD, and Shy-Drager syndrome (one cause of laryngeal abductor failure) are also associated with apnoea.

⁴¹⁸ Severe sleep apnoea is an independent risk factor for ischaemic CVA in older people.(Munoz ea, 2006)

⁴¹⁹ The **central type** (known as *periodic breathing* if there is hypopnoea instead of apnoea) is due to respiratory centre dysfunction secondary to diminished cardiac output associated with cerebrovascular disease. Symptoms resemble those of the peripheral/obstructive type. It may lead to hypertrophy and fibrosis of heart muscle, declining cardiac function, arrhythmias, hypertension, and CVA.

snoring, daytime drowsiness⁴²⁰, and, in childhood, enuresis. Other symptoms include unrefreshing sleep, restlessness or choking during sleep, morning headache and drunkenness, reduced libido, and ankle oedema. Boring activities may induce attacks. Long distance lorry drivers are often overweight and suffer from obstructive sleep apnoea. Transient, mild sleep apnoea may occur during pregnancy. The road traffic accident (RTA) rate of patients with obstructive sleep apnoea is up to 7 times greater than that of normal drivers. The condition resembles hypertension in that there is a continuum from normality to severe abnormality. (Stradling, 1989) Physical examination may show obesity, narrowing of the upper airway⁴²¹, and, rarely, disorders of the brain stem. The main complications are nocturnal arrhythmias, hypertension⁴²², and, again rarely, polycythaemia and cor pulmonale. Patients with sleep apnoea may represent problems for anaesthetists, especially after nasal surgery when packs are used. (den Herder ea, 2004)

The best treatment, not often achieved, is weight reduction. (Peppard ea, 2000) Nasal continuous positive airway pressure (CPAP⁴²³) is effective but may be cumbersome. CPAP treatment of sleep apnoea in patients with heart failure reduces systolic blood pressure and improves left ventricular function, (Kaneko ea, 2003) and reduces the risk of serious cardiovascular events. (Marin ea, 2005; Bradley & Floras, 2009) If the patient remains sleepy during the day despite CPAP a trial of modafinil (Provigil) may prove beneficial. Other approaches include sleeping in lateral or face up position, avoiding respiratory depressants (alcohol - probably causes hypotonia; hypnotics), correcting any anatomical abnormality of the upper respiratory tract⁴²⁴, losing weight (Johansson ea, 2009), muscle tone improvers such as theophylline or protryptiline or respiratory stimulants like acetazolamide, and, rarely, bypass of obstruction with tracheostomy.

Patients with sleep apnoea or chronic obstructive pulmonary disease who are hypoxic tend to have greater oxygen desaturation during REM sleep; by reducing REM, protryptiline may be helpful in such cases. (Moxham & Costello, 1994) SSRIs are helpful in some cases, independent of any REM effect. (Doghranji, 1998) Indications for treatment in mild elderly cases include excessive sleepiness, cognitive impairment, or associated cardiorespiratory abnormalities. (Prinz ea, 1990) A dramatic resurgence of REM sleep may occur early during effective treatment of sleep apnoea.

Garrigue ea (2002) point out that many patients with sleep apnoea have nocturnal bradycardia, paroxysmal tachyarrhythmias, or both. Permanent atrial pacing can prevent these. They found that those patients who received atrial overdrive pacing at a rate of 15 beats/min above baseline rate had a significant decrease in the number of episodes of central or obstructive sleep apnoea without reducing total sleep time. This procedure might work by reversing excess vagal tone.

Sleep apnoea may be more common in children than was thought heretofore. (Stores, 2000) Most cases are not obese, children may be overactive by day, apnoeic events are less frequent and of shorter duration than in adulthood, and enlarged tonsils and adenoids are a common underlying cause.

Sleep-related laryngospasm

Episodes of abrupt interruption of sleep with sensation of suffocation followed by stridor
Can exhaust the sufferer

Aetiology obscure but some cases seem to be caused by gastro-oesophageal reflux and may respond to treatment of this disorder

Cheyne-Stokes respiration

Impaired respiratory centre response to CO₂

Associations: left ventricular failure, CVA, cerebral atherosclerosis, head trauma

⁴²⁰ **Daytime sleepiness** can be measured with the *Epworth Sleepiness Scale*. (Johns, 1991) The scale poses certain scenarios (e.g. sitting and reading) and asks the patient to score 0-3 for the likelihood of becoming sleepy during them. A score > 9 on a 0-24 scale is abnormal (sometimes confusingly expressed as 5 +/- 4). E.g. severe obstructive sleep apnoea might score 16 and narcolepsy might give a higher score.

⁴²¹ Tonsils, S-shaped nasal septum, myxoedema, acromegaly, micrognathia. In acromegaly there an increased serum somatomedin-C level and failure of serum growth hormone levels to be suppressed to < 1 ng/ml after an oral glucose load.

⁴²² A (CARDIA) study has shown a positive relationship between reduced sleep duration and increased systolic and diastolic blood pressure. (Knutson ea, 2009)

⁴²³ **Bilevel positive airway pressure** (BPAP), an alternative approach, is different in that pressure is higher during inspiration than expiration.

⁴²⁴ Tonsillectomy. Laser-assisted uvuloplasty [LAUP], performed under local anaesthetic, has largely replaced uvulopalatopharyngoplasty, which required a general anaesthetic. Dental devices to prevent mandibular collapse or tongue protrusion during sleep.

Exacerbating: sleep, sedative/hypnotics, opioids
 Cycles of slowly decreasing in breathing leading to apnoea – increasing respiration (hyperventilation)
 Hyperventilation associated air hunger and panic

Nightmares, or bad dreams, occur during REM sleep. There is very little associated movement because of reduced muscle tone. (Yousaf & Sedgwick, 1996) If a child has a nightmare he will either wake up spontaneously or be awakened with ease by those looking after him. He will vividly remember what he was dreaming about, which often reflects some daytime event or preoccupation. Occasional nightmares are unimportant. Nightmares may accompany nocturnal hypoglycaemia, the partner noticing that the patient is sweaty and restless during sleep and the patient complaining of hangover and headache next morning. Nightmares may be troublesome in some survivors of disasters, e.g. the famous Coconut Grove nightclub fire of 1942 in Boston. (Adler, 1943) Many drugs have been reported to cause vivid dreams and nightmares⁴²⁵. Abrupt withdrawal of baclofen, a muscle relaxant, may precipitate delirium. Rehearsal of a repetitive nightmare may cause it stop if it is given an imaginary happy ending, so-called elimination of the threat through mastery. (Davis, 1985) Hartmann et al (1987) examined lifelong sufferers and reported raised scores on the 'psychotic' side of the MMPI and on the 'boundary deficit' score of Rorschach; there was also an excess of first and second degree relatives with nightmares, psychological problems, and psychiatric in-patient treatment.

*Night (sleep) terrors*⁴²⁶ and *somnambulism*⁴²⁷, occur during stage 4 of N-REM sleep⁴²⁸ and tend to occur early at night (within 2 hours): sleepwalking is most likely to occur within two hours of falling asleep⁴²⁹. Both conditions are strongly familial⁴³⁰, may be associated with daytime anxiety/stress, and can be provoked by centrally acting drugs⁴³¹. Somnambulism may occur in patients with bipolar affective disorder on a combination of lithium and an antipsychotic agent. (Cookson, 1998) Zolpidem has been reported to be associated with somnambulism. (e.g. Madden et al, 2009) Children with either terrors or somnambulism are very difficult to waken⁴³², are confused and do not remember⁴³³ what happened. In sleepwalking, the subject, who has a blank stare, sits up and makes repetitive movements or, less commonly, walks or goes to the toilet and urinates; standing the child during stage 4 may induce walking. In a night terror, the child appears to wake in great fear but is, in fact, asleep; there may be dramatic screaming, agitation, sweating and tachycardia. They affect 3% of children between 1 and 14 years of age, are uncommon in adults, and occur only in predisposed people who usually have a family history of sleep problems. In content, 'terrors' usually involve falling, being trapped, attacked, or choking. Somnambulism may rarely be associated with violence toward others. (Oswald & Evans, 1985) An erect penis would serve as evidence against somnambulism in forensic cases. Stairs, fires and other potentially dangerous items should be made secure for somnambulists⁴³⁴. The child should not be roused from a terror as this will prolong the attack and leave the child confused. Therapy for *severe* cases aims at lightening stage 4 sleep with a tricyclic antidepressant (TCA) or a benzodiazepine (BZD), particularly clonazepam. One report of success with paroxetine was contaminated by early co-prescription of clonazepam (Lillywhite et al, 1994) but paroxetine does seem to be effective and often more quickly than any antidepressant action could account for. (Wilson & Nutt, 2008, p.

⁴²⁵ E.g. reserpine, beta-blockers, clonidine, indomethacin, alpha-methyl dopa, verapamil, baclofen, famotidine, nalbuphine, pergolide, stanozolol, nicotine (patches), digoxin (toxicity), and withdrawal from hypnotic drugs such as BZDs, alcohol, barbiturates, and opiates. Note that pergolide (and carbergoline) are ergot derivatives and may cause serosal reactions (e.g. retroperitoneal fibrosis) and pergolide has been implicated in restrictive valvular heart disease.

⁴²⁶ *Pavor nocturnus* in children, *incubus* in adults.

⁴²⁷ Sleepwalking.

⁴²⁸ Both disorders can be exacerbated by sleep deprivation. (Morin & Edinger, 2007, p. 614)

⁴²⁹ The same applies to sleep-talkers.

⁴³⁰ And concordance is greater in monozygotic than in dizygotic twins. Pockets of high prevalence of night terrors and somnambulism have been discovered, e.g. in the descendants of Welsh people who emigrated to Patagonia. (Wilson & Nutt, 2008, p. 53) Familial somnambulism may be associated with excess of DQB1*05 and DQB1*04 haplotypes (DQB1 genes are also associated with narcolepsy and REM sleep behaviour disorder).

⁴³¹ Lipid soluble beta-blockers, some TCAs, and some BZDs. Alcohol may precipitate night terrors and somnambulism. Shift work, alcohol, neuroleptic drugs, stimulants, and antihistamines may induce somnambulistic episodes.

⁴³² Whereas nocturnal panic attacks call full awakening.

⁴³³ Unlike nightmares, which are recalled.

⁴³⁴ Unfamiliar environments carry intrinsic dangers, e.g. the not uncommon situation where a person sleeping in a hotel falls out of the window presuming it to be a door (as at home)! (Wilson & Nutt, 2008, p. 54)

55) Clonazepam may cause daytime hangover. Other suggested treatments for night terrors have included propranolol. Night terrors are benign⁴³⁵ and usually resolve within a few years, but can be very distressing. Lask (1988) suggested that parents note the timing of night terror episodes on 5 successive nights, and the presence of any signs of autonomic arousal (e.g. tachycardia). The child is then roused for 10-15 minutes prior to an episode (use autonomic arousal as timer if it is difficult to time the onset of the terror). Five minutes later the child is allowed to sleep again. This regime is continued until the terrors stop; in many cases the terrors stopped within one week; if there is a recurrence, then the treatment is continued for another week. Lask suggests that this approach can also be used for sleepwalking on its own. Apparently, it interrupts faulty slow wave sleep.

Older children with terrors may be helped by relaxation treatment or hypnosis.

Some children with terrors have medical problems (reflux, periodic limb movements, sleep-related breathing difficulties) that need attention. Sleepwalking with onset after childhood may be associated with stress, personality problems, (Sours ea, 1963; Calogeras, 1982) or medication. Sleep deprivation, migraine, head trauma, stroke, encephalitis, and hyperthyroidism can also precipitate somnambulism.

*The narcoleptic syndrome*⁴³⁶ consists of narcolepsy, cataplexy⁴³⁷, sleep paralysis, and hypnagogic/hypnopomic hallucinations⁴³⁸. The full 'tetrad' is found in under one-tenth of cases of narcolepsy. Nocturnal sleep fragmentation⁴³⁹ and even insomnia are other aspects of the syndrome.

Extremely short (seconds) micro-sleep periods may occur that are not noticeable to either patient or onlooker. Total sleep duration per 24 hours is not increased in narcoleptic subjects.

Cataplexy: Laughter, anger or surprise may precipitate cataplexy⁴⁴⁰, a paralysis of voluntary muscles; the patient, whose jaw and head drop and whose knees become weak, may fall to the ground, mute but fully awake; sufferers are often awake during brief cataplectic episodes, whereas longer episodes merge with sleep and the EEG shows REM phase characteristics. Prolonged attacks may be accompanied by visual hallucinations. Cataplectic attacks may be focal/partial⁴⁴¹ or generalised. The affected parts may twitch as muscle tone gradually returns. The condition responds to TCAs like clomipramine, but the SSRIs are preferred because of their side effect profile. There is some evidence for efficacy for mirtazepine and venlafaxine. Sudden cessation of antidepressants should be avoided because of the potential danger of precipitating episodic or continuous cataplexy⁴⁴².

Rare cases of familial cataplexy without narcolepsy have been reported.

*Narcolepsy*⁴⁴³: Narcolepsy usually begins in childhood or early teens (age range: 5-70, rare after 40). The commonest victim is a young male. About one in 2,500 of the population have narcolepsy⁴⁴⁴, a disorder of REM inhibition: the sufferer enters REM sleep on falling asleep; sleep-onset REM periods have also been reported in depression, sleep apnoea, disturbances of the sleep-wake schedule, drug and alcohol withdrawal, and some structural brain lesions.

Suggested diagnostic criteria for narcolepsy

Average sleep latency of < 5 minutes
REM onset within 5 minutes of falling asleep
CSF hypocretin-1 level < 110 pg/ml

⁴³⁵ Cases starting beyond childhood are thought sometimes to be early harbingers of temporal lobe epilepsy.

⁴³⁶ Or *Tetrad of Gelineau*, after the French physician, Jean-Baptiste-Édouard Gelineau (1859-1906), who described it in 1880.

⁴³⁷ By right, narcolepsy should be narcoplexy (Gelineau confused catalepsy and cataplexy, as do many modern practitioners).

⁴³⁸ 25-30% of narcoleptics have such hallucinations: auditory, visual, or occasionally somatic.

⁴³⁹ Many awakenings.

⁴⁴⁰ Cataplexy may be exaggerated by enjoyment, fatigue, poor sleep, sporting activity, coughing, sneezing, sexual activity, or simply blowing ones nose.

⁴⁴¹ E.g. head dropping, object dropping, knee weakness, or double vision from involvement of neck, hand, or external eye muscles.

⁴⁴² *Status catalepticus* comprises continual cataplectic episodes over hours. It can be spontaneous or evoked (by the emotional response to cataplexy itself or by stopping antidepressant treatment for cataplexy). Cataplexy is similar to the atonia of REM sleep. (Dauvilliers ea, 2007)

⁴⁴³ Term first used in 1880 by Gelineau.

⁴⁴⁴ Doherty ea (2010), who believe that narcolepsy is 'hugely under-diagnosed' in Ireland, give a prevalence of 25/100,000. The Japanese may have a higher susceptibility to narcolepsy. (Morin & Edinger, 2007, p. 611)

Controversially, Douglass *et al.* (1991) believed that about 7% of patients with 'schizophrenia' really had narcolepsy. However, schizophrenia-like disorders do appear to be more common in narcoleptics than in the general population, (Davison, 1983) and narcoleptic patients with hallucinations may be misdiagnosed as having schizophrenia. (Aldrich, 1990; Haba-Rubio, 2005) Hyde and Lewis, (2003, p. 190) believe that the 'association between narcolepsy and psychosis most likely reflects a side-effect of amphetamines used in treatment, rather than the disease itself'. Langdon *et al.* (1984) found that all of 37 patients with narcolepsy expressed the major histocompatibility complex antigen HLA (human leucocyte antigen) DR2⁴⁴⁵ compared with 21.5% of 200 normal controls, linking narcolepsy with the short arm of chromosome 6. (Langdon *et al.*, 1984) More specifically, almost 100% of cases are associated with DQB1-0602 and DQA1-0101 HLA antigen genes. (Mignot *et al.*, 1994) Forty to eighty percent of patients with multiple sclerosis are DR2 positive, as are 20% of the British white population. One to two percent of typical narcoleptics do not have the DR2 haplotype, although related findings are found on analysis of restriction fragment length polymorphisms. In general, it can be said that HLA DR2 and DW2 haplotypes are markers for narcolepsy. (Hobson & Silvestri, 1999) These findings suggest the possibility of an autoimmune process. Six candidate genes for narcolepsy discovered in a genome-wide association study (Shimada *et al.*, 2010) are NFATC2, SCP2, CATNA1C, TCRA, POLE, and FAM3D.

Most cases of narcolepsy appear to be sporadic, (Linkowski, 2002) although such cases may have an underlying genetic susceptibility. Westphal, in 1877, reported narcolepsy occurring in a mother and son. Since then familial narcolepsy has been described; some dog breeds (e.g. Doberman pinchers) suffer from familial narcolepsy; narcoleptic phenomena also occurs in mice. Focal lesions of the posterior hypothalamus are a rare cause of narcolepsy.

Orexins/hypocretins⁴⁴⁶ are novel neuropeptides produced in the lateral hypothalamus⁴⁴⁷. Orexin is involved in the sleep-wake cycle and CNS arousal.⁴⁴⁸ Canine narcolepsy (autosomal recessive with full penetrance⁴⁴⁹) is associated with mutations in the orexins/hypocretins receptor-2 gene.⁴⁵⁰ Hypocretin-1 levels are reported as very low or undetectable in the CSF of narcoleptics (Nishino *et al.*, 2000; Dalal *et al.*, 2001), the serum concentration of the same substance has been reported to be normal in such cases, (Dalal *et al.*, 2001) and postmortem studies of narcoleptic patients have shown a loss of orexin-containing cells in the peri-fornical hypothalamus. (Thannickal *et al.*, 2000) The cause of hypocretin cell loss is unknown. (Dauvilliers *et al.*, 2007) Knockout mice⁴⁵¹ lacking orexins/hypocretins show episodes of behaviour arrest. The same neurons that produce orexins/hypocretins in mice are activated by modafinil. (Taheri & Hafizi, 2002) Modafinil may inhibit the dopamine transporter. (Wisor & Eriksson, 2005)

Two parts of REM sleep occur separately while one is awake: muscle atonia and presleep dreaming. Narcolepsy is essentially an overpowering desire to sleep. Short episodes of sleep are repeated frequently and, with time, such naps may become less restorative and nocturnal sleep may become disturbed. Sleep can occur at awkward times or in dangerous places. During an ordinary night's sleep the narcoleptic is prone to myoclonus, broken sleep, and pulse and breathing abnormalities. Patients may have disturbing dreams and may complain of sensing a 'presence' in the room. Narcoleptics have problems at work, in marriage, in industry, and in traffic throughout life. There is a tendency to increased BMI and even obesity. (Schuld *et al.*, 2000)

Some cases experience episodes wherein they continue an activity but do so less efficiently, e.g. writing muttering, gibberish, or missing turns when driving; on recovery, the sufferer has no recall for the events that transpired during the episode.

⁴⁴⁵ Also called HLA DRw15.

⁴⁴⁶ Orexin was demonstrated in brain in 1998; in fact, orexins and hypocretins are the same, but were discovered by different researchers independently: orexins A and B are also known as hypocretins 1 and 2 respectively.

⁴⁴⁷ With projections to the monoaminergic and cholinergic parts of the ascending reticular activating system.

⁴⁴⁸ Release of hypocretin increases during waking hours, more so if the person is active. Levels also rise during REM sleep but reach a nadir during non-REM sleep.

⁴⁴⁹ Penetrance is the probability of manifesting a phenotype given a particular genotype.

⁴⁵⁰ Two hypocretin receptors, hcr-1 and -2, have different affinities for the 2 hypocretins.

⁴⁵¹ Mario Capecchi, Martin Evans and Oliver Smithies won the 2007 Nobel prize in physiology or medicine for their work on knockout mice. Knock-out, knock-in, and traditional transgenic mice are genetically engineered mice with genetic material removed from a particular locus, inserted into a particular locus, and randomly inserted (not into a particular locus) respectively.

Frequent daytime naps may reduce the need for stimulant drugs.(Aldrich, 1990) Amphetamines⁴⁵² or methylphenidate (Ritalin; a piperazine derivative of amphetamine) are used in treatment These agents were assumed to show a 'paradoxical' calming effect in children (barbiturates, but not antipsychotics, may stimulate children) but this mechanism seems unlikely.

Gamma-hydroxybutyrate (sodium oxybate) has been used for insomnia in narcolepsy⁴⁵³ but it has to be taken a number of times during the night; it has been abused by athletes (increased slow-wave sleep increases growth hormone secretion) and alcoholics,(Caputo & Zoli, 2007) and as a euphoriant.(Nishino ea, 1998) It is helpful for daytime somnolence and sleep attacks and cataplexy.(Littner ea, 2001)

Modafinil (Provigil, 100 mg and 200 mg tablets), a new non-amphetamine stimulant with possibly low abuse potential or tendency to induce tolerance,(Buguet ea, 1995; Anonymous, 2004) 200-400 mgs./day (100 mgs./day in elderly) in divided doses (morning and noon), can cause severe renal and hepatic impairment, suggesting that lower doses (100-200 mgs./day) may be safer. Interestingly, it is not recommended for children. It should be used with care in anxious patients. Blood pressure and heart rate should be monitored in hypertensives. Modafinil, the first specific compound for narcolepsy, should be avoided in people with left ventricular hypertrophy or ischaemic ECG changes, chest pain, arrhythmia, or mitral prolapse. Modafinil induces cytochrome P-450 isoenzymes⁴⁵⁴ so that at least 50 µg of ethinyloestradiol needs to be given in anovulants to prevent contraceptive failure⁴⁵⁵. Like St John's Wort, modafinil may lower cyclosporine levels. Although adverse data is lacking, caution is advised with co-prescribed TCAs. Care should also be taken when combining modafinil with anticonvulsants. Adverse effects of modafinil include anxiety, agitation, aggression, central stimulation, headache, insomnia, anorexia, abdominal pain, nausea, gastric discomfort, dry mouth, palpitation, tachycardia, and tremor. Occasionally a pruritic skin rash appears, and very rarely one may encounter buccofacial dyskinesia.

Psychotic symptoms attributable to amphetamines may abate when the dose is lowered or the medication is changed to modafinil.(Vourdas ea, 2002) Interestingly, an actigraphic⁴⁵⁶ study in schizophrenia recorded increased motor activity attributable to modafinil.(Farrow ea, 2006)

*Periodic leg/limb movements*⁴⁵⁷: In this disorder there are abrupt stereotypic and periodic flexion of the legs and feet associated with repeated awakenings throughout the night. Incidence appears to increase with age. It does not occur during REM sleep. Feet may be very hot or cold. Sleep apnoea is a common accompaniment. Antidepressants, including SSRIs, can exacerbate the condition.(Buisse ea, 1996) Dopaminergic drugs, including short term L-DOPA use, and carbamazepine are helpful. Eighty percent of patients presenting with restless legs syndrome also have periodic limb movement disorder.

*Sleep starts*⁴⁵⁸: Brief benign sudden limb or neck movements occur on falling asleep. A person awakened by hypnic jerking may experience *siderealism* (feeling as if falling in space). A similar picture may be caused by nocturnal or fragmentary myoclonus and hyperekplexia syndrome (startle disease⁴⁵⁹).

Idiopathic hypersomnolence is the commonest of the primary hypersomnias. The patient cannot wake up fully for hours after rising. He remains confused and disorientated, so-called sleep drunkenness, and complains of prolonged and deep nocturnal sleep. Many sufferers have diurnal periods of automatic behavior. Small doses of a stimulant are helpful. Most patients are DR2 positive, suggesting a genetic relationship with narcolepsy.

Menstrual-related hypersomnia involves excessive daytime sleepiness for some days prior to menstruation. It may improve with anovulants.

Painful legs, moving toes: Continuous unilateral pedal sinusoidal flexion-extension with ipsilateral leg pain whilst awake, with continuation during sleep at a reduced intensity, usually associated with peripheral nerve lesions such as in the lumbar roots. *Painful arm, moving fingers* is a similar disorder.(Verhagen ea, 1985)

⁴⁵² Which may potentially stunt growth by speeding up epiphyseal crossing: monitor child's height.

⁴⁵³ As Xyrem in the US.

⁴⁵⁴ 1A2 and 3A4 induction and inhibition of 2C isoforms.

⁴⁵⁵ A second non-hormonal method of contraception can be suggested.

⁴⁵⁶ **Actigraphy** uses a piezoelectric movement detector (actometer) worn like a wrist watch and allows recording of information for up to four weeks.

⁴⁵⁷ Formerly called *nocturnal myoclonus*.

⁴⁵⁸ *Hypnagogic* or *hypnic jerks*.

⁴⁵⁹ A rare disorder in which myoclonus follows minor stimulation during sleep or whilst awake.

Circadian rhythm sleep disorders can be divided into delayed sleep phase syndrome, advanced phase syndrome, non-entrained type, irregular sleep-wake type, and shift work type (QV).

Delayed sleep phase syndrome: This circadian rhythm disorder may affect up to 10% of insomniacs attending sleep disorders clinics. It typically starts in adolescence or young adulthood and is often familial. The patient cannot get to sleep until after everyone else and, if allowed, sleeps on that much later. Structural polymorphisms on one of the haplotypes of the period-3 gene (*hPER3*) have been implicated in this disorder: a long allele favours morning preference and a short allele favours evening preference. Hypnotics are generally ineffective, only producing drowsiness. Bright light exposure in the morning and light restriction in the evening may help. There have been positive reports for melatonin and for vitamin B12.

Where sleep phase is *advanced (advanced sleep phase syndrome)* treatment is by evening exposure to bright light. Some such cases are due to a mutation in the period-2 gene on chromosome 2q⁴⁶⁰.

The phase-response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. (see box)

In the *non-entrained circadian rhythm sleep disorder* (see *hypnocytohemeral* or *non-24-hour-day* or *free-running syndrome*) there is a progressive delay of the sleep period over days. It was originally described in the blind but can occur in the sighted.

The *irregular sleep-wake type of circadian rhythm sleep disorder* was described in physically sick people who spent years in bed and were socially isolated. However, it is more likely to be seen in association with intellectual disability, brain damage, and dementia. There is an absence of any pattern to sleeping and waking, patients sleeping for a few hours at irregular intervals. This may lead to complaints of poor sleep and tiredness.

Bright light v melatonin (Dagan & Borodkin, 2005)

Bright light in the morning causes phase advance

Bright light in the evening causes phase delay

Melatonin in the morning causes phase delay

Melatonin in the evening causes phase advance

Interpersonal and social rhythm therapy (IPSRT: Swartz & Frank, 2008) is aimed at helping patients regulate their social rhythms and to manage interpersonal relationships in the hope of reducing the risk of developing depressive and manic moods. Three strategies are interwoven in IPSRT: interpersonal psychotherapy (e.g. managing role transitions), psychoeducation (e.g. daily mood ratings and information about the illness), and social rhythms therapy (e.g. adapting to changes in routine and searching for triggers that disrupt rhythms). The therapist 'blames' the mood disturbance and not the patient for the latter's dysfunction and suggests that (as well as psychosocial stress) predisposed people may be made more vulnerable to mood disorders by disruptions in circadian rhythm. The interpersonal psychotherapy (IPT) component includes an exploration of the dynamics of relationships with past and present 'important others' in the patient's life. In addition to areas normally included in IPT the IPSRT therapist seeks 'grief for the lost healthy self' (e.g. the person I would have been without the illness and how can I adapt to having a chronic disorder). The 'social rhythm metric' is a paper record of daily activities and help needed in doing things chronicked by the patient. The therapist recommends very gradual re-scheduling of activities such as time of going to bed, e.g. 5-minute extensions.

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⁴⁶⁰ FASPS (familial advanced sleep phase syndrome) gene near telomere of 2q; autosomal dominant (one family has genetic polymorphism in *hPER2*): morning larks; sleep, melatonin and temperature rhythms brought forward four hours.

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6

Basic sciences⁴⁶¹**Brian O'Shea***'There is nothing wrong with wanting to make the world a better place, but utopianism has its dangers'.* (LeFanu, 1999)*'Most of life is qualitative: we use numbers simply to facilitate our understanding of it, not to define it'.* (Duffin, 2000)**Psychology**

Psychology, the *scientific study of behaviour and mental processes*, is discussed only briefly here; aspects of medical psychology will be discussed as they arise throughout the text.⁴⁶²

Perception is the active, automatic process whereby patterns of sensory stimuli are changed by the nervous system into a conscious experience. Knowledge and experience are then brought into play in order to bring meaning to what is experienced. The brain maintains perceptual constancy by combining what is experienced via the senses⁴⁶³ with previous knowledge. However, our interpretations of what we experience via the senses is open to bias from preconceived ways of thinking and classifying (schemas). Figure-ground differentiation is a classic example of how the same sensory data can be interpreted differently depending on what part of an image one chooses to emphasise: the famous (central) chalice/goblet and (peripheral) faces (looking at one another) that adorn so many psychology texts. Lower cognitive ability measured on enlistment into military service at mean age 20.4 years was associated with increased risk of depression, generalised anxiety disorder, alcohol abuse or dependence, and post-traumatic stress disorder assessed by structured diagnostic interview at mean age 38.3 years. (Gale et al, 2008)

Grades of intellectual disability by IQ⁴⁶⁴

⁴⁶¹ There follows an overview of some basic science issues of special interest to psychiatrists. Prescribing for the pregnant and nursing mother is discussed here for convenience. When reading North American literature, the reader should be aware of spelling (e.g. foetus versus fetus), abbreviation (e.g. hs means nocte in the US), and name (e.g. paracetamol versus acetaminophen, or adrenaline versus epinephrine) differences from what are found in these islands. Trade names may differ entirely or by as little as one letter from one country to another. Pharmacologists use the words uptake and reuptake interchangeably. Neurotransmitter typing changes rapidly and no book can claim to be up to date.

⁴⁶² The interested reader is referred to Atkinson et al (1996), Gross (1996) and Mowbray and Rodger (1978)

⁴⁶³ Often partial information, unusual views of objects, varying distance from objects, body movement, etc.

⁴⁶⁴ **Some examples of genetically determined disorders associated with intellectual disability** (do not expect full syndrome in every individual case):

Fragile X syndrome: dysfunctional FMR-1 gene at Xq27.3 (trinucleotide repeat: CGG); most common inherited cause of intellectual disability (1 in 4,000 boys – *Down's syndrome is genetic but is not inherited*); moderate to severe intellectual disability, long face, prominent forehead and jaw, large ears, macro-orchidism, hypotonia, seizures, ADHD, pervasive developmental disorder, affected females can show full severity range; tremor-ataxia in boys; premature ovarian failure in girls.

**Fragile X syndrome.**

Turner's syndrome: 1/3,000 female births (others are miscarried); females with only one X chromosome; gonadal dysgenesis (no secondary sexual characteristics), infertile, short stature, webbed neck (congenital lymphoedema), broad flat chest, bicuspid aortic valve, coarctation of aorta, hypothyroid, kidney problems, difficulties with vision and hearing, problems with doing more than one task simultaneously, poor social skills, poor at mathematics, 90% have IQ in normal range, and depression as adults.

Mild – IQ 50-70 (80% of cases)

Moderate – IQ 35-49 (12%)

Severe – IQ 20-34 (7%)

Profound – IQ < 20 (< 1%)

Distribution of Intelligence

IQ = (mental age/chronological age)X 100. Average IQ = 100 (< 70 = intellectual disability; > 130 = superior). The left side of a graph showing IQ in a population is higher than the right side. People represented by the extreme left side usually have pathological causes for low IQ. Those with higher IQs than the 'pathological' group are affected by many genes acting in concert and also by sociocultural deprivation. People with mild intellectual disability account for 2% of the population, those with lower IQs accounting for only 0.4%.

Because IQ measurement error is 5 points it is possible for someone with an IQ of 75 to be intellectually disabled if he/she is unable to adapt to demands. Likewise, a person with an IQ of 65 might be sufficiently adaptive to negate a diagnosis of intellectual disability.

Intelligence tests

Tests used should correlate strongly with overall intellectual function⁴⁶⁵ or involve batteries that specifically assess intelligence⁴⁶⁶.

Problems

- based on a particular population that was used originally to standardise the test, e.g. the WAIS was originally based on Americans between 16-64 years of age; the WAIS-R-UK is an adaptation for British use although many norms are still American
- personality variables such as motivation and persistence
- inability or refusal to concentrate
- fear of failure
- confusion
- anxiety, depression, etc

Uses

- to measure degree of intellectual behaviour
- to detect specific learning deficits and assets
- to detect organic brain lesions
- to follow progress of intellectual deterioration⁴⁶⁷
- research, e.g. effects of diet, environment or other factors on IQ
- To detect influences of IQ on risk of developing psychiatric illness⁴⁶⁸

Klinefelter's syndrome: 1/600 live male births; often recognised at puberty; affects males with one or more extra X chromosomes (sex chromosomes fail to separate at meiosis); shy, lacking in confidence, tall stature, long legs, small testes, gynaecomastia, infertile, low testosterone/high FSH and LH, increased rate of ADHD and some aspects of psychosis (e.g. hallucinations).

Williams syndrome: microdeletion at 7q11.23; elfin facies, short stature, stellate iris, pulmonary artery stenosis and other cardiac defects, mild-severe intellectual disability, good verbal ability, reduced response of amygdala to new faces, somatisation, narrow interests, and obsessiveness.

Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency): The condition arises from mutations in the DHCR7 gene (11q13.2-q13.5) that makes 7-dehydrocholesterol reductase, an enzyme involved in the first step in cholesterol synthesis. Cholesterol is needed for normal development of the embryo and is part of the structure of cell membranes and is found in myelin. It is also important in the synthesis of some hormones and gastrointestinal acids. The infant is hypotonic, has feeding difficulties, and grows slowly. Syndactyly and, less often, polydactyly may be found, as may anomalies of various internal organs. There is a distinct facies (e.g. broad nose, small lower jaw, and low-set ears), microcephaly, and a low IQ and behaviour problems.

Smith-Magenis syndrome: microdeletion at 17p11.2; mild-moderate intellectual disability, broad, square-shaped facies, prominent forehead, deep-set eyes, short nose, tenting of upper lip, relative prognathism, short hands/fingers/feet, deafness, hypotonia, skeletal problems, impulsiveness, poor sleep, temper tantrums, aggressiveness, pull own nails and pick at skin, self-hugging, and stereotypies.

Duplication 15: extra chromosomal material within chromosome 15 (mainly 15q11-14) or as separate mass; findings vary with amount of duplicated material and paternal origin of abnormal and normal chromosomes; infantile spasms, ataxia, hypotonia, genitor-urinary problems, low IQ, pervasive developmental disorder; may have Angelman syndrome (happy disposition, developmental delay, severe intellectual disability, seizures, ataxia) or Prader-Willi syndrome.

⁴⁶⁵ E.g. the *National Adult Reading Test* (NART) or the *Wechsler Test of Adult Reading* (WTAR).

⁴⁶⁶ E.g. the *Stanford-Binet Intelligence Test* or the *Wechsler Intelligence Scales*.

⁴⁶⁷ Lack of multiple versions of the WAIS can lead to misleading results if the test is repeated too soon after a previous session.

⁴⁶⁸ Koenen et al (2009) found lower childhood IQ was associated with increased risk for schizophrenia spectrum disorder, adult depression, adult anxiety, greater comorbidity and persistence of depression and possibly of generalised anxiety disorder, and

Self-esteem (a personal sense of efficacy, self-regard, hope, and confidence) is developed from infancy onwards. Parents accept and admire their babies which allow infants to begin to develop a sense of self-value. If youngsters are required to perform tasks that are outside their capabilities they will fail at the task, will not receive positive feedback and self-esteem suffers.

Paternal influences on the psychosocial development of children may have been relatively neglected by researchers. Most paternal psychiatric disorders increase the risk for behavioural and emotional problems in their offspring, probably to a similar degree to that stemming from such disorders in the mother. There is some indication that sons may be more adversely affected than daughters and that behaviour may be more disturbed than emotions. (Ramchandani & Psychogiou, 2009) Pathways for risk transmission include genes, poor parenting, and effects on the mother. Of course, paternal effects are modified by other variables such as child factors (age, sex, and temperament), maternal parenting and psychopathology, degree of paternal presence, and economics.

Personality is discussed elsewhere. Jean Piaget⁴⁶⁹ (see box), described four stages of cognitive development in children: sensorimotor (so-called because sensory impressions are closely linked with motor activity – starts with reflex gaze and grasp in newborn and ends with attempts at thinking about a problem at up to two years), preoperational (symbolism to metacognitive regulation at 8 years), concrete (from classification to simultaneity at 9-11 years – concreteness is well illustrated by asking a child to relate a joke: limited grasp of nuances impairs the ability to do so), and abstract reasoning (hypothetical deductive logic, etc).

Piaget's developmental stages

Sensorimotor – 0-2 years – information received via senses and motor activity – no reflective or conceptual thinking – knows an object as something that can be manipulated in certain ways

Preoperational – 2-6 years – development of symbolism (including language) – one object can stand for another object – egocentric (chiefly sees matters from own viewpoint and assumes others feel and think in the same way as does the self) – can only consider one dimension (e.g. confuses volume and height of liquid in different receptacles)

Concrete operational – 7-11 years – can understand and use logic; interprets objectively instead of intuitively; can use multiple perspectives; uses concepts e.g. conservation (such as preservation of volume despite moving liquid between receptacles of different heights), taxonomy (classification, e.g. houses, animals), and seriation (e.g. arranging objects by size) – still mostly confined to consideration of that which is tangible

Formal operations – 11 years onwards – can think abstractly and consider hypotheses; can look at a variety of outcomes/possibilities; absolutism gives way to relativism; can grasp motivations and principles; can apply principles to solve new problems

Piagetian theory has been modified over the years (researchers are now better at couching tasks in age-friendly ways) and it is now accepted that children can understand more than they can say. (Shapiro & Hertzog, 2003) Piaget also considered moral development. At first everything is black or white, wrong or right, and rules are not to be questioned. Later on the child understands that strict adherence to a rule might have adverse consequences. Finally the child understands fairness and reciprocity.

Memory involves registration (storage is not guaranteed), storage (retrieval is not guaranteed) and retrieval (possible only if information has been stored). Psychologists divide memory into sensory (lasts little longer than the stimulus producing it), short-term (a small number, averaging 7, pieces of information, held for up to half a minute), working memory (more complicated than short-term memory and is required for the carrying out of complex cognitive work), and long-term memory (potentially limitless information held for

increased risk of adult mania. Is this explained by premorbid low IQ as an integral part (including consequence) of early illness (or tendency to same), low IQ among carers, or poor coping powers (leading to referral)? Urfer-Parnas et al (2010) in a Danish draft-board study found that all future individuals hospitalised with (various) mental disorders had lower premorbid IQs than controls and in each diagnostic category decreasing IQ was associated with increasing risk of becoming a patient (odds ratios 0.5-2.5 over the full IQ spectrum).

⁴⁶⁹ Piaget (1896-1980) was a Swiss psychologist.

very long periods of time). Semantic memory involves information such as one's first language whereas episodic memory is concerned with personal data.

Lesion studies in monkeys suggest that various parts of the prefrontal cortex⁴⁷⁰ are required for the performance of different tasks that test working memory. (Liddle, 2001, pp. 30-32)

In order to retrieve information it must have been stored in some accessible and logical manner. One can use recall in the relative absence of cues, i.e. one actively searches for an answer⁴⁷¹. We may recognise a correct answer from a list of possible solutions without being able to generate it in the absence of the list. Relearning what has apparently been forgotten usually takes less time than was the case at the first attempt. 'Re-constructive' memory is a term applied when a person retells a story learned from someone else; as it passes on details tend to change. This is well known to criminal lawyers! Redintegration refers to the triggering of memory traces when one hears a certain sound or experiences a particular smell⁴⁷². Retrieval of information may be aided by context (e.g. revisiting the site of a crime) or state (e.g. remembering what happened when last intoxicated with alcohol when again in an inebriated state).

Theoretically, stored information may be unavailable because of so-called passive decay (chemical or structural changes), distortion of information, or interference (two similar stored items create confusion). These theories of 'forgetting' are just that: theories.

Cognition and growing old (Anderson, 2008)

Changes are mild but a large industry has grown up selling 'cures': *Ginkgo biloba*, procaine products, Nintendo puzzles, etc

Older people react more slowly than do younger subjects

The more demanding the situation the greater the difficulty in coping – unfamiliar tasks⁴⁷³, having to think through a problem, and having to come up with strategies cause the most problems

Two types of intelligence: fluid and crystallized (Horn & Cattell, 1967)

Fluid intelligence – use of reason to find structure in a problem and apply appropriate strategies to solve it

Crystallized intelligence – use of learned methods of solving tasks

Verbal IQ (depends on crystallized intelligence) preserved better than performance IQ (depends on fluid intelligence) with ageing

Older people are less flexible and strategic in their thinking – less able to abstract structure from a problem and at employing feedback to grasp rules and concepts

Novelty is more of a challenge

Preservation of problem-solving when over-practiced skills are required

Preservation of immediate memory (e.g. telephone number) and established bank of knowledge

Reduced ability to learn new information that can be recalled later – performance on paired associate⁴⁷⁴ learning tests of Wechsler Memory Scale declines gradually from mid-life

Support (cues) during learning improves formation of long-term memory

The more difficult the test the more obvious will be deficits in recognition tests

Naming difficulties are more likely with uncommon words and proper nouns: tip of the tongue phenomenon

⁴⁷⁰ The **prefrontal cortex** (PFC) does not function in a vacuum. It has important interconnections with the striatum, thalamus, and the medial temporal lobe, so that lesions in these areas (e.g. amygdala) or disconnection from these areas may mimic PFC lesions. The PFC may be divided into orbitofrontal (important in regulating emotional activity), medial prefrontal, and dorsolateral (DLPFC) cortices. The medial prefrontal cortex (MPFC) sends input to, among other areas, the periaqueductal gray (PAG) and stimulation of the lateral column of the PAG (by excitatory amino acids) leads to raised heart rate and blood pressure and diminished pain perception (part of the 'attack mode'). The ventral MPFC has been dubbed the *visceromotor cortex* because of its effects on cardio-respiratory and alimentary function. The ventral MPFC is activated at rest and deactivated during cognitive tasks which suggests that it has a role in monitoring the body's internal state during rest. Craving for a drug of abuse induced by environmental cues (e.g. a room where the drug was consumed in the past) appear to be transmitted to the nucleus accumbens shell via the MPFC. The DLPFC is important for working memory.

⁴⁷¹ If a patient gives accurate answers with the help of prompting the likelihood is that he has a problem with retrieval (fronto-subcortical circuitry) rather than a storage (hippocampal) problem.

⁴⁷² The author has noticed the same in relation to drawings or paintings he has done in the past – looking at them brings back a flood of memories surrounding the time of the drawing/painting.

⁴⁷³ Alzheimer's disease also affects familiar and practiced skills and knowledge.

⁴⁷⁴ Two paired words, e.g. 'sponge-trumpet'. Easier pairs have been introduced since the original test was developed, e.g. 'knife-fork'.

Greater difficulties in following conversations involving multiple participants, especially when the topic is not familiar

Reduced spatial intelligence from mid-life onward – increased difficulty in heavy traffic or an unfamiliar shop – these are probably influenced by demand on memory

Working memory, an elaboration of short-term memory, is used in solving and understanding problems, i.e. brief storage of information in the service of current cognitive activity; a limited amount of data is kept immediately accessible for current employment or manipulation. It consists of an articulatory/phonological loop that holds data in mind by using sub-vocal speech, a visuo-spatial scratch pad that maintains data as visual images, and a central executive that directs ‘slave systems’ such as the visuo-spatial scratch pad (the inner eye) and the articulatory (phonological) loop (‘inner voice’). The central executive appears to occupy the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate (ACC)⁴⁷⁵ and the slave systems lie posterior to the central fissure: parietal (spatial), temporal (language/knowledge) and occipital (visual) lobes. Cognitive changes in old age might be a consequence of a disruption in the ACC/DLPFC network⁴⁷⁶.

Neuropsychological assessment⁴⁷⁷ involves applying standardised measures to define the relationship between suspected brain impairment and associated behavioural and cognitive accompaniments. Many instruments are used in this endeavour, e.g. the age-appropriate *Wechsler Intelligence Scale* and the *Halstead-Reitan*⁴⁷⁸ *Neuropsychological Test Battery*. The present *Halstead Impairment Index*, a global measure of brain dysfunction, looks at abstract reason (Category Test), a Tactual Performance Test (blindfolded patient places blocks into holes in a board), fine motor speed (Finger Tapping Test), ability to distinguish musical rhythms (Rhythm Test), and a Speech Sounds Perception Test (after hearing nonsense words on an audiotape the patient underlines printed response on answer sheet).

Motivated behaviour, by definition, has a purpose and is directed at a specific goal. It has been ‘explained’ by theorists varying from the humanists who write about self-actualisation to the psychoanalysts (unconscious drives), behaviourists (learning/reinforcement), cognitive theorists, and neurophysiologists. Primary drives (e.g. hunger) are necessary for mere survival and will force one to behave in a way that satisfies those drives (e.g. foraging for food). Secondary drives are those that are said not to satisfy a physiological need; play is often given as an example of a secondary drive but play teaches the animal many skills that may be necessary for efficient functioning and hence survival. Behaviour is in fact much more complicated than any of our attempts to explain it.

Girls are said to be more sociable and interested in others, whilst boys may be more content to play alone. It has been suggested that these characteristics are exaggerated in schizophrenia and contribute to the higher frequency of negative symptoms in male cases. (Castle & Murray, 2002)

Learning theory concerns the behavioural underpinnings of learning, the latter relating to more or less enduring changes in behaviour that can be observed objectively. Learning arises from experience and is not innate. In *classical (respondent or Pavlovian) conditioning* there is the pairing of two stimuli, usually a reflex (e.g. salivation on smelling food) with a neutral response. Ivan Pavlov’s dogs at first only salivated (unconditioned response, UCR) when given food (unconditioned stimulus, UCS). A bell (conditioned stimulus, CS) was paired with sufficiently often that it eventually elicited salivation (conditioned response, CR) on its own (without food being presented). Stimulus generalisation occurs where a similar conditioned stimulus generates the same conditioned response, as when different bells elicit salivation. If the bell is presented on a sufficient number of occasions without the presentation of food it will lose its power to elicit

⁴⁷⁵ See Andreescu et al. (2009): anxious depressed elderly use the ACC more intensely than do elderly with depression only when performing a cognitive task designed to activate these brain areas.

⁴⁷⁶ In old age, reduced performance appears to be related to under activation of DLPFC and overactivity of the temporal and inferior frontal cortices (word recognition/speech). Activity may not be task-focused and distractibility is relatively common. There is frontal volume loss, demyelination, and reduced synaptic density as well as diminished lateralisation of hemispheric function. Fronto-striatal circuits (involving thalamus and basal ganglia) may also play a role in executive function and the speed of thinking. (Hedden & Gabrieli, 2004)

⁴⁷⁷ **Factors that may affect results of neuropsychological tests** include the effort expended by the patient (motivation), the premorbid ability of the patient, education, occupation, experience, psychic distress, psychiatric disorder (e.g. depression, anxiety), medication (e.g. benzodiazepines), somatic health, and factors in the tester (qualifications, experience, scoring or interpretation errors). (Simon, 2005, p. 599) For an introduction to cognitive assessment see Hodges. (2007)

⁴⁷⁸ In 1947, Ward Halstead of Chicago published work on many patients with frontal lobe damage. In 1955, Ralph Reitan, Halstead’s pupil, modified Halstead’s battery to include laterality, to measure aphasia, and to take account of aging effects.

salivation, so-called *extinction*. Removal of the subject from the experiment following extinction for some hours will lead to recommencement of salivation, *spontaneous recovery*⁴⁷⁹. Skinner, influenced by fellow-American Edward Thorndike⁴⁸⁰, developed *operant (instrumental or Skinnerian) conditioning*, i.e. an animal⁴⁸¹ (or person) *operates on* the environment and the behaviour is instrumental in leading to consequences. If every time a dog presses a lever it receives a pellet of food it will be more likely to repeat the behavior than if no food was received. Reinforcers are stimuli that increase the chances of a behavioural response happening before their presentation and can be primary (stimuli meeting biological needs, e.g. thirst) or secondary (one has to learn their value – they are not inborn, e.g. financial reward). Reinforcement may be positive (pleasant) or negative (removal of an aversive stimulus such as an electric shock). Punishment (e.g. giving an electric shock every time an unwanted behaviour occurs), on the other hand, is less effective in *shaping* (reinforcement of successive approximations what is desired) behaviour. There are a number of possible reinforcement schedules: continuous (every time the response occurs it is reinforced), partial (only some responses are reinforced), fixed interval (regular reinforcement, e.g. every X seconds), fixed ratio (a fixed number of responses are reinforced), variable interval (regular but unpredictable reinforcement), and variable ratio (regular reinforcement but with a change in the number of required responses with each sitting). The last two, variable interval and ratio are powerful forms of reinforcement, it being very difficult to extinguish the new behaviour. Pathological gambling is sometimes explained as stemming from lack of ability to predict the next win (variable ratio reinforcement schedule) but this tells us more about why the behaviour is maintained rather than why it starts in the first place. *Observational learning*, championed by Bandura⁴⁸², is learning by observing (*modelling*) rather than doing and is of great importance in child development. *Insight learning*, championed by Kohler, states that learning is a cognitive process and not dependent on the simple trial and error implicit in stimulus-response theories of Pavlov and Skinner. Normal adults can override conditioning (lose the CR) if they are informed that the unconditioned stimulus will not occur; otherwise the CR would extinguish slowly. Language is on the side of the adult, a fact reflected in the current trend toward cognitive-behavioural instead of pure behavioural approaches.

Anthropology

The Concise Oxford Dictionary defines anthropology as '*the study of mankind, esp. of its societies and customs; study of structure and evolution of man as an animal*'. Foulks, ea (1977), and Keshaven, ea (1989) are useful sources on anthropological psychiatry.

A person lives within a culture and is expected to live by its rules. Psychopathology *per se* causes considerable personal and socio-economic disability across cultures. (Ormel ea, 1994) Delusions are influenced by culture; they may be highlighted or partially hidden by different cultures. Psychoanalysts, such as Jung, drew extensively on cultural myths in their thinking and writings about the evolution and behaviour of men. On the other hand, to say that someone is from a particular country, although subject to stereotyping, tells us very little about him. Comparisons between cultures of the epidemiology and manifestations of various psychosocial variables and disorders are of help in increasing our understanding of such dysfunctions as long as both the cross-sectional and longitudinal diagnoses are fundamentally similar⁴⁸³. Witness the claim for a better outlook, in the sense of a low relapse rate, for schizophrenia in developing countries, and the dispute as to whether some cases diagnosed as schizophrenia should in fact be diagnosed as brief reactive or acute and transient psychoses. (Susser ea, 1995) Poor tolerance levels, high expressed emotion (EE) levels, or environmental demands might affect western schizophrenic patients adversely. (O'Shea, 1997) Urban Indians with schizophrenia, when compared to those in Cincinnati, were

⁴⁷⁹ The extinction of CS is suppressed rather than eliminated – this may go some way to explaining why abstinent addicts resume drug use when re-exposed to the drug. Other 'explanations' include memory, hedonism, peer pressure, emotional immaturity, etc.

⁴⁸⁰ Thorndike worked with 'puzzle boxes' and found that a stimulus-response connection was 'stamped in' if an animal received pleasure from an act and was 'stamped out' if no pleasure followed the act, the so-called *law of effect*.

⁴⁸¹ Originally rats in Skinner's experiments. There is no conditioned stimulus in operant conditioning: no stimulus is presented before an operant response that led to the behaviour.

⁴⁸² Bandura's **social learning theory** posited that there were cognitive mediating variables (e.g. self-esteem, self-monitoring, and self-efficacy) between a stimulus (S) and a response (R), i.e. the 'black box' was active. It was simply S – R but rather S – Cognition – R. Pathological gambling might start when a (vulnerable?) person observes others gambling and be maintained by variable ratio reinforcement scheduling.

⁴⁸³ Yang and Link (2009) suggest that difference in prevalence rates of disorders between studies may be explained by response rates since mental disorders may be more prevalent in non-responders.

more often married, employed, cared for by their families (versus community mental health services), and more compliant with drug therapies.(Dani & Thienhaus, 1996) Attendance at a day centre may mitigate the effects of high EE relatives.

Members of the same culture share many things in common, e.g. beliefs, attitudes, and ways of evaluating and categorising. Similarly, members of the same culture usually describe perceived stimuli with the same words. Cultural beliefs such as possession by ghosts should not automatically lead to a diagnosis of psychiatric disorder. The meaning of the experience for the patient and the community should be ascertained from the family, using a local interpreter if required.(Jadhav, 1995)

Institutions may contain a therapeutic atmosphere or they may breed dependence. Lack of independent social activity within a mental hospital is largely a result of a complex interaction of the social atmosphere and the incapacity of illness. Mental illness exists in all cultures, albeit in modified form. The poorer, less educated sectors of society in developed countries, and a much larger part of Third World populations, tend to shun psychological explanations and presentations of their distress and to express it in somatic terms, as if 'a weight on my shoulders' became 'a pain in my neck'! Porter (2001, p.86) points out that the word pain is derived from the Latin for punishment (*poena*), a notion at least as old as the Bible which 'construed pain as the penalty for disobedience'.

Various cultures believe in non-medical causes of mental illness, such as witches, spells, sorcery, breaches of taboo, soul loss, and possession by demons.(Last, 2004; El-Adl ea, 2008) An element of this is to be found in all of us. Hence the success of the horror movie, the persistence of certain avoidance behaviours like not walking under a ladder or, in women, not wearing green to a wedding, and the employment of lucky charms such as a rabbit's foot. Folk healers abound in most cultures; e.g. 'cures' handed down by grandparents, the seventh-son-of-a-seventh-son, and shamans. Quite often such healers are noted for some personal characteristic, such as disfigurement, great age, or scholarship. Much ritual is involved, often involving a participating public audience. The depth of belief in the efficacy of such interventions is illustrated by the fact that a sick shaman will seek the help of a fellow shaman.(Magner, 1992, p. 9) In Africa, the mentally ill are sometimes required to live for long periods at the healer's home.(Karim ea, 1994) *Rootwork* (e.g. voodoo rootwork) refers to a belief that illness is caused by a curse/spell/hex/evil eye, witch, sorcerer, or some other ill-intentioned person. Some cultures shun doctors in favour of local healers while others may utilise both.(Cole ea, 1998)

Illnesses, mental or physical (e.g. tuberculosis), were, and sometimes still are, often seen as been sent directly by God, sometimes as punishment for the sins of relatives. The Irish call the mentally handicapped the 'Children of God'.

It is not unusual for a patient to seek help from a doctor, a priest, and a faith healer simultaneously or at different stages of his illness. The Church sometimes practices exorcism, although much less often today. The concept of Original Sin holds that we are prone to sickness because of the sin of our First Parents. It is increasingly important that we try to understand and get on with faith healers, as long as the health of our clients is not harmed thereby.

When making a diagnosis in someone from another culture certain confounding variables should be borne in mind.(Littlewood & Lipsedge, 1988) Among these are selective pattern of migration; experience of migration and 'status' striving in a climate of low opportunity; culturally determined response to adversity; patterns of service utilisation (non-recording of birthplace may confuse hospital admission statistics); and diagnostic accuracy of our techniques when applied to other cultures. Longitudinal studies of immigrant populations are essential.

According to Bhugra and Ayonrinde,(2004) susceptibility to mental disorder among migrants can be divided into vulnerability (biology, psychology, social skills deficits, forced migration, persecution, negative life events, bereavement, culture shock, cultural conflicts, and discrepancy between what is achieved and what it was hoped would be achieved) and protective (psychology [e.g. resilience], high socioeconomic status, voluntary and adequately prepared migration, strong cultural/ethnic identity, and social support/networks) factors, both being divisible into those operating before, during and after migration. Family dysfunction and migration have been reported to interact in the histories of children and adolescents with psychosis.(Patino ea, 2005)

People with severe mental disorders who are caught up in a disaster setting may have their condition exacerbated by stress, lack of medication, and loss of normal social support.(Jones ea, 2007) The most important intervention is to see to their basic needs.

Mental health problems in *refugees*⁴⁸⁴ are discussed by Saraceno et al. (2002). The most commonly reported disorders are post-traumatic (PTSD), mood, anxiety, and adjustment disorders. It is to be expected that many refugees would show suspicion, excess vigilance, anxiety, and fearfulness. Psychoses and disorders of childhood and adolescence (PTSD, depression, anxiety, conduct disorder) are also prevalent. Some authors suggest that PTSD is over-diagnosed in refugees and that a grief model may often be more appropriately applied. Religious faith, political beliefs and being psychologically prepared are protective. Information is lacking on exactly when psychotic states start in refugees, i.e. before or after becoming a refugee. Longterm follow-up of Vietnamese refugees in Norway (Vaage et al., 2010) suggests that self-reported psychological distress may decline significantly over time but that a substantial number still have symptoms after almost a quarter of a century of resettlement. *Koucharang*, a culture-bound syndrome found in Cambodian refugees, is defined as excessive thinking following exposure to traumatic events. *Bebatchel* is a depressive state found among the same people under similar circumstances. Children absorb a new culture quicker than do their parents, a fact that may lead to their being required to handle social problems for their elders.

Problems associated refugee status

Problems in old country:

Threat to lives/security of self/loved ones
 Loss of relatives, friends, community, property, occupation, physical health
 Trauma including torture, rape, head injury (perhaps with epilepsy)
 Forced dislocation, concentration camp experiences
 Precipitation/exacerbation of mental disorder

Problems in new country:

Detention⁴⁸⁵
 Insecure residency⁴⁸⁶, adaptational problems, racial discrimination, poverty, poor housing, unemployed⁴⁸⁷, barriers to accessing services, family disruption/violence
 Precipitation/exacerbation of mental disorder: anxiety, depression, grief, dissociation, somatisation, impulsivity, substance abuse
 Cultural transference/countertransference⁴⁸⁸

Abbreviated version of 'The Mental Health Service Requirements for Asylum Seekers and Refugees in Ireland' of the the College of Psychiatry of Ireland, March 2009⁴⁸⁹

The asylum process needs to be rigorous in order to be fair to legitimate asylum seekers. Many genuine cases are treated as economic migrants. Asylum seekers are placed in a position of dependency on others. Their skills and qualifications may atrophy, because they are barred from employing them. This can contribute to loss of self-worth. As self-esteem declines they can become less assertive in seeking basic human rights and necessary medical health care. A Dutch report found that if the asylum process was extended beyond two years there was a doubling of psychiatric illness. Insecure residency and associated fears of repatriation contribute to persistence of psychiatric symptoms and associated disabilities. The RCPsych recognised 3 main areas of state action needed in relation to asylum seekers and refugees: a stated and enacted public policy that minimises the impact of social risk factors for physical and mental illnesses; equitable access to a full range of health, social care and legal services (both for ease of access and to ensure that individual needs are delivered in a coordinated manner services are best provided together at a designated centre); public bodies should deliver such care to standards required by national and international law. In 2002, the Irish Psychiatric Association (IPA) recognised that treatment of asylum seekers is highly specialised and involves particular skills not normally found in conventional mental health settings. This is especially so for asylum seekers who have experienced torture. The IPA recommended that services should be improved so that adequate and appropriate mental health interventions could be delivered to this vulnerable group stating. The policy of dispersing asylum seekers around Ireland to avoid ghetto formation and to hasten integration into the wider community may unwittingly lead to the social isolation of asylum seekers. This may aggravate any underlying mental health difficulties. Asylum

⁴⁸⁴ The 1951 *UN Refugee Convention* defined a refugee as an 'eligible' person who seeks foreign asylum because of a legitimate fear of persecution because of ethnicity, race, political affiliation or religion, at home. Immigrant refugees may be kept in such miserable conditions in the host country (Anonymous, 2010) that it would be surprising if they went unscathed.

⁴⁸⁵ This appears to have negative effects on mental health and there is evidence of some (but incomplete) improvement following release. (Robjant et al., 2009)

⁴⁸⁶ Particularly high levels of depression have been associated with being an illegal Hispanic in the USA. (Oquendo et al., 2004)

⁴⁸⁷ E.g. qualifications may not be recognised.

⁴⁸⁸ Positive or negative transference/countertransference based on perceptions of the other person's ethnic background, e.g. excessive curiosity or suspicion, or excessive therapist anger as a reaction to past trauma experienced by the patient.

⁴⁸⁹ Original document prepared by Izu Nwachukwu, David Browne, and John Tobin on behalf of the Faculty of Adult Psychiatry, College of Psychiatry of Ireland.

seekers have little say in where they are placed. They can become dislocated with little chance to develop social networks. They may be forced to live in accommodation with asylum seekers of other nationalities with whom they share little in common. Such geographical spread impedes development of expertise in the treatment of asylum seekers.

The *Irish Times* (May 5, 2008) reported that there were 6,844 asylum seekers living in 62 accommodation centres around Ireland in April 2008. Their asylum seeking status precluded them from obtaining work. They were provided with accommodation, food and €19.10/week. As they await the results of the protracted process of being granted asylum they are caught in a situation of dependency and idleness that can erode self-esteem. This may lead to substance abuse as a consequence of boredom and may aggravate underlying mental health problems that may exist. Current arrangements for asylum seekers in Ireland leave them in a situation of controlled poverty. 2,798 immigrants were held in Irish prisons during 2003 and 2004. Two-thirds of those imprisoned were held there in excess of 51 days during 2004. *SPIRASI*, a non-profit, non-charging agency accredited by the International Rehabilitation Centre for Torture Victims, is attempting to fill the void in service provision for asylum seekers. *SPIRASI* treated 892 victims of torture from 66 different countries during 2007. Because of current financing stringencies they now confine referrals to North-East Dublin. *SPIRASI* (in their communications with the College of Psychiatry of Ireland) has emphasised the need for a professional network of interpreters and the requirement to train staff in how to work with interpreters. They have noted a tendency among the medical profession to inappropriately diagnose asylum seekers as mentally ill because of a lack of cultural awareness.

In a questionnaire prepared by the Irish College of Psychiatry in 2008 (completed by 57 consultant psychiatrists) the great majority of respondents recognised that asylum seekers were a particularly difficult group to treat and most felt they were insufficiently resourced to cater for specific needs in this area. Because of the complexity of such cases a higher level of mental health assessment and care is needed than is the norm. This complexity arises from language barriers, problems with obtaining suitable translators, a lower level of trust among asylum seekers when dealing with authority, time constraints, and cultural barriers to talking about areas such as being victims of torture, intimidation, physical/sexual/emotional abuse.

Half of the respondents felt that asylum seekers were over-represented at their community mental health clinics relative to their actual number within their catchment areas. There was a willingness to prepare the necessary medico-legal reports required for the asylum process and to provide the best quality service that they could deliver. They believed that the HSE did not recognise that asylum seekers had special mental health needs and the necessity of the extra resources required. Clinics were already overburdened and under-resourced in caring for the current indigenous population. There felt that they did not have adequate resources to liaise with outside agencies with responsibility for asylum seekers. There was an acceptance that the psychiatric reports that they were already providing require a high input of time and effort. The need to collect collateral information and adequate and appropriate translation services placed high demands on clinical time. There was consensus that special skills are needed and that transcultural psychiatry must be developed further.

Recommendations: 1. Consultant led multidisciplinary teams with special interest in mental health of asylum seekers and refugees to be established in the major urban centres. 2. Special interest section on transcultural psychiatry should be established within the College of Psychiatry of Ireland. 3. The College or other appropriate organisations should provide training courses on the preparation of psychiatric reports on asylum seekers. 4. There must be rapid access to mental health care and high quality social and legal services for unaccompanied minors. 5. Prisons should not be used as places of detention for people with legal difficulties related to their immigration status.

Some important terms are defined in the box.

Some useful terms

Acculturation: assumption of characteristics of larger or more advanced society.

Acculturation problems: difficulties in adapting to a different culture or environment that cannot be attributed to a coexistent mental disorder.

Actualisation: realisation of one's full potential.

Alloplastic adaptation: adapting by changing the environment (alloplastic = externalised).

Assimilation: total absorption in the larger society, and therefore calling for greater change than in acculturation.

Autoplastic adaptation: adapting by changing own behaviour and responses.

Culture: a set of values, norms, beliefs, and understandings common to a human group.

Cybernetics (Gk. for steersman): study of control systems and communications in animals and machinery.

Ecology: science of organisms as effected by their environment; human ecology applies ecological principles to the study of human societies.

Ethnicity: a person's sense of belonging to a human group who share the same origin, history, and culture.

Ethnography (Gk. *ethnos*, race): examination of written records, folk tales, myths, language, key informants, life histories, questionnaire surveys, psychological tests, and participant observation in order to study cultural forms.

Ethology: study of animal behaviour, including its origins; classically studied in natural settings, but increasingly performed in experimental situations; associated with the Austrian Konrad Lorenz (1903-88), Karl von Frisch (1886-1982) and Nikolaas Tinbergen (1907-88), a Dutch zoologist based in Britain.

Multiethnic countries: an example is the USA; however, the values of the white middle class predominate (WASP: White Anglo-Saxon Protestant).

Sun dance and spirit dance: practices of certain Native American tribes to focus on personal, group, ancestral and behavioural issues; those engaged in the spirit dance must abstain from drugs and alcohol. *Sweat:* water is poured over hot rocks in a confined place by Native Americans; the resultant steam is used for prayer, cleansing and healing.

Sociology⁴⁹⁰

'The more a form of behaviour deviates from current social norms the more likely are its perpetrators to differ from the rest of the population'. (Sims, 1992)

'...governments are dependent on their electorates, who too often resist the allocation of more services and resources to poor families and communities'. (Heath, 2002)

'The key to promoting youth mental health is through strengthening of the fundamental nurturing qualities of the family system and community networks while explicitly acknowledging the rights of young people'. (Patel et al, 2007)

The Concise Oxford Dictionary defines sociology as the *'science of the development and nature and laws of human (esp. civilized) society; study of social problems.'* It is the study of how groups of people organise themselves.⁴⁹¹ Man is a social animal.⁴⁹² He has a uniquely long period of dependence and immaturity⁴⁹³.

Western adolescents are expected to walk a thin line between responsibility for the self (individuation) and being responsible to their elders. In many 'underdeveloped cultures, the transition to adult responsibility is less obvious. Early relationships are extremely important in determining how the final product, the adult, functions. Highly developed Western societies have more nuclear (parents and immediate offspring only) than extended (grandparents and other relatives) families; this, and broken relationships, significantly reduce the available pool of family carers. (Drury, 2005)⁴⁹⁴

Starting at home with his parents, the child begins to view himself as others do, to learn what he is permitted to do and what is frowned upon, and to learn how to act in concert with others as part of a group. We all assume or are designated roles within society. Such roles are a function of biology (e.g. father), education (e.g. barrister), and the needs of the self (e.g. patient) or of society (e.g. military conscript). These roles may be partly or completely a result of our own choice, e.g. priests, redundant labourer. However, even when they seem to be wholly our own doing they may have been primed by numerous other factors acting independently of us, e.g. failing markets, religious parents. Middle class parents encourage an internal locus of control in their children. Working class parents are more likely to teach a more passive message.

We internalise the norms and values of our society. Nevertheless, subgroups within the same society may vary widely in terms of what is seen as acceptable behavior and what constitutes reprehensible acts. Labelling (individual characteristics ascribed meaning by others), e.g. as a troublemaker, may force conformity to such roles on the individual. Societies, which measure success, perhaps financially, may be so structured as to erect barriers against the attainment of goals for some members, and so they promote deviancy. Hence we have terms such as 'subcultural sociopathy'. Some sociologists lump criminal conviction and applying a psychiatric diagnosis together as acts whereby a label of primary deviance (from what society expects) is given to individuals. This deviance is then amplified (secondary deviance) by the changes that follow in the labelled individual's behaviour. Thus, both legal and medical authorities are responsible for alienating individuals, i.e. creating forcing people to adopt deviant styles and paths in life. There is undoubtedly some truth in this but, at least in part, the flaw may be in applying the result to

⁴⁹⁰ The burden of mental and personality disorders in society is reflected in the early onset of most such conditions. For example, the median age (in years) of onset in the **Epidemiologic Catchment Area (ECA) Study** in the USA (Robins et al, 1991) were as follows: antisocial personality disorder, 8; phobias, 10; somatisation disorder, 15; drug abuse, 18; schizophrenic and manic episodes, 19; OCD, 20; alcohol abuse/dependence, 21; panic disorder, 23; and major depression, 25. The ECA looked at > 20,000 adults in 5 cities in the USA (community and institutional); trained interviewers used the *Diagnostic Interview Schedule* to determine DSM-III diagnoses; individuals with a lifetime history of a mental disorder had odds ratios of 2.3 and 4.5 for lifetime history of alcohol use disorder and drug use disorder respectively. (Regier et al, 1990)

⁴⁹¹ Useful early references include Hudson (1982) and Keeper (1987). The word 'therapy' comes from *therapeutae* (Gk.) meaning small extended family villages organised to deliver assistance to poor and disabled people.

⁴⁹² Apart perhaps from those of us with schizoid personality disorder.

⁴⁹³ This has been lengthened somewhat in modern society by education and apprenticeship

⁴⁹⁴ The 'typical' nuclear family with 2 parents and 2.5 children and the father acting as breadwinner is actually atypical in modern England, comprising just over one-quarter of households in 1991. According to official sources, (HMSO, 1991) twenty-five percent of households were one-person households in that year and the number of young persons living in such homes had been increasing at a greater rate than old people in such circumstances had. Also, by then, most married women worked outside the home.

medicine alone rather than to a problem with civilisation. Avoiding a necessary diagnosis does not make it go away and psychiatrists are more aware than ever of their obligations in terms of keeping their restrictions on individual liberty to what is necessary in the patient's interest and also their crucial role in areas such as enabling, promoting recovery, and fighting stigma, lack of resources, and inequalities. Some societal attitudes have changed over the years. The author remembers well when tuberculosis and cancer, not to mention homosexuality, were subject to the same stigma as mental illness. A major aim of the medical profession is to improve the efficacy of our interventions, an important way of reducing the fear associated with diagnosis!

Social support⁴⁹⁵ (types of) – help provided by others (relatives, friends, school, work, professionals)

Esteem – respect and positive statements ('You can do it!') increase self worth

Emotional – the concern and warmth offered by others

Informational – pertinent information helps one to cope more effectively

Instrumental – direct assistance, e.g. what are ones entitlements such as how/where to get a widow's allowance

Social support following violent crime victimisation (Andrews ea, 2003)

Both sexes report equal receipt of positive support

Females received more negative responses from close others than did males

Negative responses predicted PTSD at 6 months, especially in females

The happiness of people depends, at least to some degree, on the happiness of others with whom they are connected. (Fowler & Christakis, 2009) Western family changes promote distancing from certain support systems and greater reliance on psychiatry. (Gilbert, 1999, p. 52) Social support, such as integration into the community and having a confidante, protect against illness, (Segal & Phillips, 1967) and lack of it seems to promote depression⁴⁹⁶ and anxiety. (Mirza & Jenkins, 2004) Perceived low social support and living alone increased the likelihood of using primary and mental health services in the Netherlands. (Have ea, 2002) Women undergoing hysterectomy benefit from such support. (Robinson, 2000) In a 10-year follow-up in Oslo, (Dalgard ea, 1995; 1997) the buffering effect of social support may only apply to those people with an external locus of control⁴⁹⁷ (feel powerless and lacking in control over their own lives). Those with an internal locus of control do not have the same need for social support in order to cope with life's stresses, and have low symptom scores even when negative life events are combined with weak supports. The buffering effect of social support was especially strong for depression. Kendler ea (2005) point out that women have higher rates of major depression than men, but they also have stronger, more intimate social networks! However, they found that emotional support protected women more than men from major depression. An internal locus of control is more highly valued in individual oriented Western society with its emphasis on the autonomy of the person than it is in traditional societies where decisions are made by the family. (Okasha, 2002) Social changes probably play a vital role in reports from America (Cole ea, 1998) and elsewhere of increasing 'depression' and suicide (Atakan & Davies, 1998) as well as substance and alcohol abuse among younger age groups. Casey and Craven (1999) state that large scale attempts at reducing the suicide rate may be more of a socio-political and religious issue than a medical one. It is often not realised that psychiatric patients in general have increased standard mortality ratios for all three major classes of unnatural death: suicide, homicide, and accidents. (Hiroeh ea, 2001) Young children of parents with mental illness may also have elevated mortality risk, particularly for unnatural causes of death. (Chen ea, 2010)

Coping with illness (Laubmeier ea, 2004; Schlozman ea, 2008)

⁴⁹⁵ See Cobb (1976). The term **social capital** refers to trust and give-and-take among neighbours as well as a tendency to stand by one another. It also refers to education, having a job or the possibility to train for one, and retention of family ties.

⁴⁹⁶ Whilst a twin study suggested that one may inherit attributes that attract social support (Schoevers ea, 2000; Agrawal ea, 2002) the study lacked sufficient power (low numbers) to detect shared environmental effects.

⁴⁹⁷ *Locus of control* was described first in 1966 by Julian B Rotter (b. Brooklyn, NY). Compare with *sociotropy* (defining ones worth by reference to interpersonal relatedness) and autonomy (sense of worth derives from attaining ones goals and being independent and a free agent) from Beck. (1983) In patients with schizophrenia an external locus of control, whilst not specific to their disorder and more related to personality, does correlate with less periods of wellness and with depressed mood. (Harow ea, 2009)

Coping involves a response to and a method of dealing with difficulties - these may have good and bad effects not only on the patient but also on those caring for the patient

Illness is a burden carrying risks and threats

Reactions are often disproportionate to objective danger

Uncertainty about how one will cope is a common source of distress

For some patients being sick provides a favoured alternative to the responsibilities of wellness; such patients may complain excessively and blame those caring for them

Determinants of coping include the problem itself and the availability of internal (mental, emotional, somatic) and external (financial, social, organisational) resources

Existential issues such as 'why me' and death must be struggled with

Religion may offer peace, meaning, hope, and improved prognosis

Good communication between patient and the treating team may defuse problems and promote coping

Psychiatrists may be used by other professionals to take on the burden of dealing with difficult patients

Successful copers have high morale and are optimistic even when progress is uneven; they deal with issues as they arise and have a flexible, broad array of approaches to problem-solving and can weigh up likely outcomes; they listen to advice and are able to pace themselves

Unsuccessful copers are rigid, intolerant, inflexible and unable to lean on others when necessary; their ability to focus on the problem at hand is sub-optimal and may have strongly held preconceptions; they may latch on to questionable advice; denial and rationalising are common; passivity smothers initiative; and responses may sometimes be chaotic and impulsive

Feral children, those who are reared away from humans, are intellectually backward and have a distorted identity. (Itard, 1801) Women who recollect poor early maternal care may be poor at relating, marry early, have poor quality marriages, and be divorced from a previous marriage. (Birtchnell, 1993)

The way in which children are reared and corrected in the home varies widely between social classes, with physical chastisement being more likely among the working classes and verbal approaches predominating at the top of the social ladder. (Newson & Newson, 1970) Regardless of socio-economic status, alcohol, cannabis and tobacco abuse is more common in the children of parents who leave them alone at home for long periods. (Richardson ea, 1989) A Swedish group (Weitoft ea, 2003) found that children who grew up in a single parent family had excess mortality, severe morbidity, and injury, even when household resources were taken into account. Lone mothers⁴⁹⁸ suffer from an excess of depression and material disadvantage. (Targosz ea, 2003) Lone mothers were more likely to have psychiatric disorders and to have experienced physical and sexual violence than were partnered mothers in one Australian cross-sectional survey. (Butterworth, 2004) Violence was a better predictor of psychiatric disorder than were being a lone parent or having a particular socio-demographic profile. Cooper ea (2008) found that psychiatric disorders could be explained by financial problems in lone mothers but not in lone fathers; the former had an excess of such problems but lone fathers were even more likely to have them.

Children of psychiatric patients are often adversely affected across a wide range of functions; they are often ignored in routine anamnesis; parents may fear being blamed and having their offspring removed from their care; and a significant minority of childhood psychiatric problems persist into adulthood. (Ramchandani & Stein, 2003)

Sexual intercourse is occurring at an earlier age than heretofore. This may be postponed by a broad based sex educational approach in schools. (Wellings ea, 1995; Mellanby ea, 1995; Bearinger ea, 2007) A broad range of psychiatric disorders, antisocial personality disorder, and substance misuse increase the likelihood of risky sexual activity, early sexual activity, and sexually transmitted disease. (Ramrakha ea, 2001)

Society often expects the elderly to hand over authority to the young, and that certain activities are given up (work, sex, and some pastimes). Such expectations may be a source of conflict. Also, while reminiscence may be enjoyed many by senior citizens, it may be irritating for others. Leaving home may be resisted tenaciously, and change of any type may be traumatic.

⁴⁹⁸ Respectively, there were 57,900 and 60,500 births in the Republic of Ireland during 2001 and 2002, of which 18,000 and 18,800 were births outside wedlock, and 2,900 and 2,700 were to teenage mothers; the number of lone parent families with children aged less than 20 years increased by 88% during 1994-2003.

*Stress*⁴⁹⁹ is ‘a situation where environmental demand exceeds a capacity for effective response’. (Fisher, 1993) There are many factors that feed into stress: life events (these do not predict type of disorder), inability to predict or escape traumatic circumstances, difficult life problems (poverty⁵⁰⁰, loss, etc), personality, (Kendler ea, 2003) genes, (Federenko ea, 2006) lack of work outside the home, and chronic high levels of ACTH and cortisol (reduced response to infection) and catecholamines (→ functional change → physical change). Stress hormones, neurotransmitters and cytokines⁵⁰¹ are among several mediators that are essential for maintaining stability (or homeostasis) through change, a process known as *allostasis*. Release of these chemicals in response to stress promote adaptation. If release is not switched off following cessation of stress, if they are excessively employed in response to numerous stressors, or if they are inadequately turned on, then the body experiences damage⁵⁰². (McEwen, 2004) Too fast changes in modern society is a source of considerable stress⁵⁰³, although such observations are not new. (Clouston, 1888) It may be that with two human beings subjected to similar stress, it is the one who feels he can control the source of stress, even if he doesn’t exercise the control, who develops less dysfunction. (Glass & Singer, 1972) The alleged reduction in suicide rates during war⁵⁰⁴ may be due to greater social cohesion, projection of hostility onto the enemy, a relative lack of alcohol⁵⁰⁵, and/or reduced levels of unemployment. Social institutions are given overt roles that may be markedly different from their latent roles. In some countries the army is meant to protect the inhabitants from external aggression but in fact it is employed to enforce conformity on the internal citizenry. Goffman’s (1961) ‘total institution’, an attack on badly run asylums, described regimes where everything is done in the one place and in a regulated fashion, where patients have no social roles and progressively lost autonomy⁵⁰⁶, and where patients and staff are kept socially apart. Nurses, the ‘culture carriers’ of the hospital, decided who should see a psychiatrist. Nevertheless, not all research points the finger at institutional environments, and patients with schizophrenia may still have negative symptoms or a ‘clinical poverty syndrome almost a decade after discharge. (Johnstone ea, 1981) Quality of care may be more influential than hospital conditions. (Coid, 1993)

Some strategies used in the face of stress⁵⁰⁷

Avoiding the source of stress – can be realistic as when a potential assailant is avoided or unrealistic as when someone stays away from essential school examinations; use of distraction or temporary withdrawal may be helpful

Help-seeking – this can be appropriate (family, friends, GP, confessor, accountant, etc) or inappropriate (e.g. advice sought from a severely dysfunctional peer or someone with extreme views)

⁴⁹⁹ Stress: Latin, *stringere*, to compress/draw tight. ‘Stress’ may indicate the *response* to extreme forces and attempts to maintain the status quo or the *stimulus* (the stress) itself.

⁵⁰⁰ **Poverty** is a risk factor for PTSD. (Muldoon & Downes, 2007) Poverty is an important correlate of mental disorder worldwide. (Patel & Kleinman, 2003) Jenkins ea (2008), in a cross-sectional survey of British private households, found that both low income and debt are related to mental illness, with the effect of income being mediated by debt. Social disadvantage is related to risk for psychosis. (Morgan ea, 2008) US employees develop depressive symptoms for different reasons depending on their financial circumstances, the poor because of job insecurity and the non-poor because of high psychological demands and low support from supervisors and co-workers. (Simmons & Swanberg, 2008)

⁵⁰¹ **Cytokines** are members of a diverse group of small proteins that change parent or other cell behaviour. They may be implicated in the genesis (e.g. multiple sclerosis) or used in the treatment (e.g. hepatitis C) of disease. Most act briefly and locally. They usually act as part of a cascade/network. Some (e.g. colony stimulating factors) act distally. Among the great array of functions attributed to cytokines are cell multiplication/repair/migration (including embryogenesis/organogenesis), angiogenesis, and immunity/inflammation/fibrosis. *Interleukin* (IL) referred to proteins that communicated between white cells but we now know that this is but one of their functions; interleukins are numbered IL-1, IL-2, etc. *Tumour necrosis factor* (TNF) includes cytokines that kill tumour cells, e.g. TNF-alpha. *Interferons* are divided into alpha and beta (type-1, antiviral) and gamma (type-2, immunostimulation, from cells such as natural killer cells and some helper T cells). *Haematopoietins* include granulocyte- and granulocyte monocyte-colony stimulating factors. Functions of cytokines include inflammation (e.g. IL-1, TNF), anti-inflammation (e.g. IL-4), specific immunity (e.g. IL-2 and interferon gamma are involved in proliferation and differentiation of T and B cells), chemoattraction (influence immune cell movement), and haemopoietic activity (stem cell proliferation/differentiation, e.g. IL-3 and colony stimulating factors).

⁵⁰² *Allostatic overload*.

⁵⁰³ Working conditions are probably becoming more stressful. (Reichenberg & MacCabe, 2007)

⁵⁰⁴ How many are reported or investigated?

⁵⁰⁵ Derived from the Arabic for essence, *Al kihl*.

⁵⁰⁶ See Biegler (2008) on the promotion of autonomy in psychotherapy.

⁵⁰⁷ Different lists can easily be compiled by readers and some examples might readily be transferred from one heading to another.

Relaxation – can be adaptive (e.g. progressive muscle relaxation, breathing exercises, yoga, music, art, light reading) or maladaptive (such as alcohol in excess)

Learning from the challenge – the positive quest for personal growth derived from mastery

Problem-solving – defining and clarifying the problem, listing options and choosing the best one, and monitoring effectiveness

Relying on past experience – drawing on relevant past personal experiences or the experiences of others

Realistic appraisal – ‘I might have only got 58% in my exam but it got me through’ or ‘If I spend more time on my weak subjects I’ll pass the exam’ or ‘Not everyone is good at that subject’

Humour – seeking a balanced perspective and releasing anxiety (not unknown in operating theatres): ‘It could be worse’, ‘I’ll have something to tell my grandchildren’, ‘You should have seen the other fellow’, and ‘McGonigle’s Correction’ (Murphy of ‘Murphy’s Law’ was an optimist – the truth is worse)

Sublimation – kicking the table instead of the boss

Reaction formation – killing a bully with kindness

Stoicism – ‘That’s life’, ‘It’s not worth being upset about it’

The ‘sick role’⁵⁰⁸ carries certain privileges, such as being excused from work, as well as obligations, such as seeking appropriate help and co-operating with caretakers. Of course, being human, we may abuse this role. The term ‘illness behaviour’ refers to the various ways in which a symptom(s) may be perceived, evaluated and acted upon, i.e. what people do when they are sick, such as being stoical or melodramatic. Such behaviour may derive from personal or observed experiences.

There were 286,129 marriages and 156,814 *divorces* in the UK in 2001. Divorcees die earlier⁵⁰⁹ and have more psychiatric (depression, anxiety, alcohol abuse) and physical illness than married people.(Richards ea, 1997) There is an increased risk of morbidity (such as depression [Gilman ea, 2003] and substance abuse [Mack ea, 2003]) for their children, particularly for a child who is less than 5 years old at the time of the divorce. The exact direction of causality is probably complex and variable between couples.(Sims, 1992; Weiss, 1998) Harper (2008, p. 24) points out that women generally have better social networks than men and are more likely to retain them following divorce, men being cut off from contacts by marital dissolution. Anyway, it is usually the woman who holds on to the children. Divorced older men may fare worse than younger males in the same situation⁵¹⁰. Older divorcees of either sex are at increased risk of experiencing poverty.(Waite, 1995)

Adoption may be associated with childhood psychological difficulties,(Ounsted & Humphrey, 1963; Mackie, 1982; O’Connor & Rutter, 2000) although prospective studies stretching into adulthood are sparse. McWhinnie’s (1967) retrospective analysis found that 10 of 58 adopted adults had suffered from mental illness. Wieder (1977) found a 15-30% incidence of adoptees in the psychiatric population compared with 2% of the general population. There may be an association with eating disorders in some instances.(Holden, 1991; McWhinnie, 1967) Children placed from care may show emotional distance, distorted expression of feelings, slow attachment formation, indiscriminate socialisation, overactiveness, opposition-defiance, and, less commonly, rage/aggressiveness.(Rushton, 2007) Rushton and Dance (2006) found that disruption (following placement from public care) was predicted by older age when placed, longer duration in care, excess behavioural difficulties, and ‘having been singled out from siblings and rejected by birth parents’. A major research difficulty is attribution of direction of causality, i.e. is vulnerability to breakdown already over represented among people presenting for adoption, or indeed among those seeking to adopt?(Mednick & Finello, 1983) Adopted patients offer unique challenges to the diagnostician who seeks a biological family history. Illegitimacy, along with new genetic mutations and low penetrance, complicate counselling.

Intercountry adoption in Sweden may be associated with an excess of suicide and attempted suicide, psychiatric admission, drug/alcohol abuse, and criminality.(Hjern ea, 2002) There are many possible reasons: poor nutrition in country of origin leading to neurodevelopmental problems, problems in the biological parents, problems in the infant that prompt referral for adoption, adoption after infancy⁵¹¹, excessive expectations of the adoptees, and racism due to having a foreign appearance. According to

⁵⁰⁸ Term dating from The Social System of 1951 by Harvard sociologist Talcott Parsons (1902-79).

⁵⁰⁹ Especially for males aged 35-45 years.

⁵¹⁰ Men are more likely to die before their wives but may spend more time alone in old age because of divorce.

⁵¹¹ Adoption during infancy was associated with better adjustment in the Netherlands.(Bieman, 1992)

Odenstad ea (2008), who looked at adoptions from abroad into Sweden and testing performed at military conscription, negative pre-adoption circumstances can have negative influences on cognitive development but the outlook could be positive if the adoptee had received good care before adoption and if adoptees were not chosen because of an excess of risk factors.

Using a modified *Edinburgh Postnatal Depression Scale* Payne ea (2010) looked at adoptive mothers during the first post-adoption year and found that the mothers may become depressed as a result of stress and problems of adjustment.

The term 'eugenics' literally translates as 'of good stock'. China's 1995 *Law on Maternal and Infant Health Care* ordered compulsory premarital examination for serious genetic diseases, some infectious diseases, and 'relevant' mental disorders. Options for those with 'positive' testing were long-term contraception or tubal ligation. Otherwise they were not allowed to marry. (Anonymous, 1995)

Family limitation methods include various forms of contraception, artificial insemination by donor, and, where available, abortion/termination. It is *abortion* in this sense that is discussed here⁵¹². The Irish Supreme Court defined 'unborn' as applying to embryos only following implantation in the womb.⁵¹³

Abortion is an emotive subject accompanied by 'strong and polarised opinions'. (Fergusson, 2008) Casey/Oates ea (2008) describe the issue as being 'primarily moral and ethical, not psychiatric or scientific'.

Legal abortions were carried out in Britain on 'women' giving an Irish (Republic) address⁵¹⁴

Year	Number
1970	261 ⁵¹⁵
1994	4,590 ⁵¹⁶
1997	5,336
1998	4,473
1999	6,214
2000	6,391
2001	6,673
2002	6,522 ⁵¹⁷
2003	6,320 ⁵¹⁸
2004	5,585 ⁵¹⁹
2006	5,042
2007	4,686 ⁵²⁰

⁵¹² About 3% of countries have a blanket ban on abortion. (Moloney, 2009) According to Ahmad (2002) world-wide there were an estimated 50 million abortions performed annually, 40% done illegally. There might be 70,000 deaths among women from unsafe abortions, and perhaps 5 million women were temporarily or permanently disabled. According to Anonymous (2007c) each year there are 210 million pregnancies world-wide, one in five end in abortion, ¾ such women live in developing countries, 97% of the 20 million annual unsafe abortions occur in developing countries, ¼ of the women are aged 15-19 years, 68,000 women die from unsafe procedures, and 5.3 million are left with temporary or permanent disabilities. Sedgh ea (2007) estimated 46 and 42 million induced abortions worldwide in 1995 and 2003 respectively; there were 31 abortions for every 100 livebirths in 2003; and 48% of abortions were unsafe and 97% of these were in developing countries. Males exceed females in China, probably because of selective abortion of females. (Zhu ea, 2009) Nicaragua banned abortion for any reason in 2008 and this seems to have had extremely adverse effects on women (death, suicide, etc). (Moloney, 2009) Blum (2009) points out that where abortion is illegal and clandestine the likelihood of the woman dying is much greater than where the practice is legal: from as high as 60 to as low as 0.6/100,000 women respectively.

⁵¹³ This definition excludes frozen embryos.

⁵¹⁴ It is unclear how many individual repeaters are counted more than once. Also, when abortion became legal in South Africa there was a huge reduction in maternal mortality.

⁵¹⁵ From 1970-93, 70,000 Irish women procured abortions in Britain. By 1995 and 2000, this figure had risen to 78,577 and 107,315 respectively. Between 1980 and end of 2005 123,258 Irish women travelled for an abortion.

⁵¹⁶ 628 of them being less than 20 years of age and 574 of whom were at least 35 years old.

⁵¹⁷ Plus 1,391 from Northern Ireland.

⁵¹⁸ Plus 1,318 from Northern Ireland.

⁵¹⁹ In addition, 1,164 went from Northern Ireland.

⁵²⁰ Plus 445 having abortions in the Netherlands, compared to 42 in 2005.

Births in Ireland outnumber Irish abortions procured in Britain by a factor of about 10. The rate for British women having abortions⁵²¹ is much higher than for Irish women. Single women outnumber other categories in abortion statistics, although Clare (2000, p. 103) would not agree. Pushing a pregnant young female to marry the child's father cures nothing and may make matters worse. (Zabin ea, 1989) According to one source, (Anonymous, 2003) about half of US pregnancies are unintended after half of the end in abortion. The Irish Medical Council approved (December, 2001) an amendment to its *A Guide to Ethical Conduct and Behaviour*, Fifth Edition 1998, recognising 'that termination of pregnancy can occur when there is real and substantial risk to the life of the mother'.⁵²² In 2009 the Irish Medical Council added a 'clear and substantial' risk of maternal suicide.

Abortion became legal in the US in 1973⁵²³. Since 1967, the law in England and Wales allows abortion act on grounds of likely damage to the health of the mother or her children. Therefore psychiatrists are less involved in evaluation, the GP or gynaecologist often making the decision about health risk. Before 1967, a serious risk to the mother's life had to be present and a psychiatrist was asked to evaluate suicide risk.

Post-abortion psychiatric problems (PAPPs)

Much research originates from societies condoning abortion (Marteau, 1993; Statham & Green, 1993)

Incidence of PAPPs (admissions or referrals) appears, from the literature, to be low, perhaps one-fifth of or equal to that associated with childbirth (Gilchrist ea, 1995)

Predisposition toward PAPPs is increased by

Younger age

Having more children before abortion

Pre-abortion psychiatric problems

Severe anxiety at time of discovery of pregnancy

Marked ambivalence about abortion

Cultural/religious prohibitions

Being forced to have abortion

'Going it alone'⁵²⁴

Woman may regret past abortion and calculate 'current' age of aborted child, especially on anniversaries of its expected date of delivery – may be more likely if woman was pressured by others into having the abortion (Ashton, 1980)

Abortion in late pregnancy may be associated with depression in a later pregnancy because of unresolved grief or because of a fear of divine retribution⁵²⁵ such that the expected baby will be deformed (Kumar & Robson, 1978)

Anonymous (1989b: review article): women who have an abortion for medical or genetic reasons⁵²⁶ and those presenting in the second trimester were thought to be more at risk for PAPPs

Abortion is associated with a 'small' (30%) increase in mental disorders among women (Fergusson ea, 2008)

Pregnancy loss *per se* (be it due to abortion or miscarriage) is associated with increased risk of mood and substance use disorders in Australian women (Dingle ea (2008)

Systematic review of literature (Charles ea, 2008): best research found no excess of psychiatric problems whereas flawed research found negative outcomes

⁵²¹ 1 in 5 English pregnancies; 0.44 per woman; mostly young, single, childless; 27% have repeat abortions according to Raleigh.(1998) The government launched a 10 year strategy in 1999 to halve teenage pregnancy in England. An English analysis of 1994-2000 showed that teenage pregnancies peaked in 1998, declining thereafter; this was associated with less conceptions and births and a 7.5% rise in abortions.(Wilkinson ea, 2006)

⁵²² This appears to be a reference to rare instances where obstetrical procedures are necessary to save the mother's life but where the baby has little prospect of survival (e.g. because of extreme immaturity), rather than condoning abortion for social reasons. In other words, the aim is to save mother, not lose baby.

⁵²³ Supreme Court: *Roe v Wade*.

⁵²⁴ I.e. not involving partner in decision/being abandoned by partner.(Lask, 1975; Stotland, 1992; Clare & Tyrrell, 1994; Gilchrist ea, 1995; Major ea, 2000)

⁵²⁵ Belonging to a faith that condemns abortion appears not to represent an insuperable barrier to seeking one.(Stotland ea, 2007, p. 349)

⁵²⁶ Abortion because of congenital anomaly or fetal death may lead to guilt or grief for the 'normal' baby that didn't happen. The partner may suffer similar feelings.

New Zealand study (Fergusson ea, 2009) found that abortion was associated with high rates of both positive and negative emotional reactions; almost 90% of respondents believed that abortion was the right decision; and number of negative responses was associated with subsequent mental health problems.

Satisfaction with abortion and negative emotions may decrease and increase respectively with the passage of time. (Major ea, 2000) Lazarus (1985), in the USA, found a low incidence of serious short-term psychiatric sequelae in a questionnaire study: the main reaction was relief, 15% had guilt and depression, and 10% found the whole experience to have been negative. Lazarus suggested counselling for certain at-risk patients, e.g. women who delay the decision to have an abortion, those with a severe psychiatric disorder prior to the procedure, and those with medical or genetic indications for termination of pregnancy. Suicide is rare in both pregnancy and after refused abortion. Gissler ea (1996) in Finland found a suicide rate in the year after abortion to be thrice that of the population rate. The first problem here is weeding out whether abortion leads to suicide or whether a common cause operates for both abortion and suicide, and the second difficulty is that the same authors report a doubling of suicide after miscarriage. There is evidence that if the mother of an unwanted pregnancy is forced to proceed to term, both she and her offspring will experience later psychosocial difficulties. (Clare & Tyrrell, 1994) Kubicka ea (2002) found that women in Prague denied abortion had children who as adults had poorer mental health than their siblings or matched controls. One might speculate that unwanted pregnancy might correlate with psychosocial difficulties in the first place. Because some women do experience psychological problems following abortion it is important that appropriate follow-up care be available. (Anonymous, 2008b) Reardon & Cogle (2002) assessed women for a depressive outcome using the National Longitudinal Study of Youth⁵²⁷: *married* women carrying an unintended first pregnancy to term were at less risk of subsequent depression than women who aborted, but rates of high risk depression scores were comparable among *unmarried* women.

In January 2002 the French Parliament adopted a bill which overturned a court ruling that had compensated a boy⁵²⁸ disabled by rubella contracted in utero. The court had held that because doctors had failed to diagnose rubella (because of laboratory error) that an abortion had not been recommended! Amid heated debate, 'medical' abortion (e.g. mifepristone) became legal in Italy in 2010.

Lack of social competence, an inability to attain and perform certain social roles, and a lack of self-confidence characterises a group of people who show increased vulnerability to mental breakdown. Social variables (status, roles, home circumstances) may be as important as severity of symptoms in determining who receives treatment and in what setting, as well as the type of label (e.g. affective v schizophrenic) and treatment (e.g. psychotherapy v drugs) offered. Social factors are also important in relation to readmission and relapse rates: lack of social supports, high levels of expressed emotion. Unemployment appears to have a real but complicated relationship with depression (Gavin ea, 2010) and suicide in both sexes, (Kreitman, 1993; Stuckler ea, 2009) completed and attempted. (O'Shea, 2000c) Suicide is high in the lowest social class anyway. Unemployment rates are a very powerful indicator of the serious mental illness requiring inpatient treatment in the working-age population. (Kammerling & O'Connor, 1993) Patients with chronic schizophrenia are affected disproportionately in the community in times of high unemployment⁵²⁹ and when the demand is for skilled workers; also, jobs have become more complicated and stressful. (Morgan & Cheadle, 1975) Butler ea (2010) found that older age and a diagnosis of schizophrenia amongst people with severe mental illness were associated with being unemployed. The best chance for the severely mentally ill, including first-episode psychosis cases (Killackey ea, 2008), getting a job is to offer supported employment (placement in competitive work while offering on the job support) rather than offering prevocational training⁵³⁰. (Crowther ea, 2001) It is illegal in Ireland, under the *Employment Equality Act 1998*, to

⁵²⁷ Begun in 1979 in the USA.

⁵²⁸ Nicholas Perruche.

⁵²⁹ And even at times of increasing employment. (Perkins & Rinaldi, 2002) *Individual placement and support* (IPS) or 'place and train' emphasises a quickly conducted job search on basis of patient preference and continuing support to patient and employer from a person who specialises in this area and who works as part of the psychiatric service. It is an effective approach. (Burns ea, 2007)

⁵³⁰ Period of preparation before going into competitive work.

discriminate against an employee because of mental health problems. The *Employment Equality Act 1998* was amended by the *Equality Act 2004*⁵³¹.

Organisational downsizing (reduction in personnel numbers) may increase sickness absence and the risk of death from cardiovascular disease in those who are left in the job.(Vahtera ea, 2004)

The role of exposure to media violence in breeding violence is controversial, with some defenders of the media suggesting that violence-prone individuals seek out violent material. This is hardly relevant in the case of minors or other vulnerable groups⁵³². The role of propaganda in spreading racism can hardly be disputed given the many examples of history. Obviously, many factors⁵³³ potentially interact in an individual to promote violence (Anonymous, 2008a) and research has been poor at weighting them, even at the population level.

The *stigma* attached to mental illness is still very strong, perhaps deeply seated in humanity⁵³⁴,(Haghighat, 2001; Warner, 2001; Eagles ea, 2003; Rutz, 2003; Angermeyer & Matschinger, 2005; Jamison, 1995, 2006; Thornicroft ea, 2007; Gurej & Kola, 2007; Mehta ea, 2009) and carries certain negative expectations, e.g. violence and lack of productivity, not to mention underfunding for services.(Dinan, 1999) Stigma may lead to poverty, poor quality of life, and marginalisation within society.(Thornicroft ea, 2009)

Stigma is present when people judge others 'not on their personal qualities but on the basis of a mark or label which assigns them to a feared or unfavoured group'.(Gelder ea, 2006, p.24)

The *Stigma Scale* (King ea, 2007) is a 28-item self-report questionnaire derived from interviews with mental health service users; it has a three-factor structure (discrimination, disclosure, potential positive aspects of mental illness); and scores are negatively correlated with global self-esteem).

Relatives of patients may conceal their association with the mentally ill (Murphy, 1999) or may experience stigma by association, especially if experiencing mental health problems of their own.(Östman & Kjellin, 2002) Media messages often reinforce negative stereotypes about mentally ill people, e.g. dangerous, odd, unpredictable.(Miller, 2007) Prejudice may involve projection of unwanted or devalued attributes onto a scapegoated group.(Lawrie, 1999) Unfortunately, prejudice is found within the medical profession, among landlords, at work,(Brosnan ea, 2002; National Disability Authority, 2002; Diffley, 2003) in the media,(Page, 1980; Alisky & Iczkowski, 1990; Jamison, 1998; Wilson ea, 2000; Mukherjee ea, 2002; Eagles ea, 2003) and even among psychiatric patients themselves – stigma directed towards self and/or others.(Swanson & Spitzer, 1970; Brohan ea, 2010) People often do not acknowledge the simple fact that psychological distress is a part of living.(Doherty ea, 2007⁵³⁵) In one Irish survey⁵³⁶ one-third of the public stated that people with schizophrenia should not have children.(Kinsella, 2010) Mental illness is too often unworthy of news coverage unless something 'spectacularly negative' happens.(Bowers, 1999; Miller, 2007) The RCPsych launched an anti-stigma campaign in which consultation and collaboration with a wide variety of people, groups and the media would be combined with an emphasis on a number of major disorders. The results were followed to see if attitudes changed.(Byrne, 1999) The results showed that severe depression, panic, or phobia carried the least stigma.(Crisp ea, 2005) McKeon and Carrick (1991) found that personal experience of depression, or depression in a friend or relative, or even visiting someone in a psychiatric hospital, engendered more positive attitudes to depression and its management. Luty ea (2007) found that didactic factsheets largely failed to alter stigma for schizophrenia and alcoholism. According to some authors,(Murphy ea, 1993; Wolff ea, 1996a) older age, low educational level, and low socio-economic status predict negative attitudes towards the mentally ill, whilst greater knowledge about the subject is associated with more sympathy and less fear. However, Crisp ea (2005) found that 16-19 year

⁵³¹ Under the former the employer had to make accommodations for disabled employees up to a nominal cost, whereas under the latter the employer is obliged to do so unless such accommodation would constitute an undue burden or hardship for the employer.(Conroy, 2005) The first successful case brought by a person who felt he was discriminated against by his employer on grounds of psychiatric illness in Ireland happened in early 2005 (almost €30,000 awarded).

⁵³² Excessive media exposure during adolescence may be associated with depression in young (especially male) adults.(Primack ea, 2009)

⁵³³ E.g. criminal activity, family breakdown/abuse, substance abuse, poverty, and some cases of mental disorder.

⁵³⁴ Quarantined individuals have problems with stigma, loneliness, isolation, a worries about their families not coping without them.

⁵³⁵ In this national survey, almost 90% of respondents would contact their GP, but only 31-48% would contact a psychiatrist, counsellor or psychologist. Most would approach family/friends.

⁵³⁶ *Public Attitudes Towards Mental Health*.

old harboured the greatest proportion of negative views, a finding reflected in male Dublin secondary school students.(Burke ea, 2008) Thornicroft ea (2009) spoke with people with schizophrenia in 27 countries and found that they were rarely in receipt of positive discrimination. Negative discrimination was common and centred around making or keeping friends, the family, finding and keeping employment, and intimate and personal relationships. Patients anticipated discrimination in job/education/training application and seeking a close relationship. 72% tried to keep their diagnosis secret. Probably related to low self esteem, people with schizophrenia did not always experience the discrimination they feared. Stigmatising attitudes in young Australians were affected by personal experiences, parental attitude and exposure to campaigns.(Jorm & Wright, 2008) Jorm and Griffiths (2008) asked Australian adults questions about four vignettes and concluded the behaviour associated with mental illness and a belief that such illness derives from a flawed character were stronger sources of stigma than are biomedical explanations. Higher education may be relatively incompatible with negative views of mental disorder.(Crisp ea, 2005) London people with children or who are Caucasian were most likely to object to community placement of the mentally ill in one study.(Wolff ea, 1996b) The provision of properly resourced services are essential in the fight against stigma (Kelly, 2005) but stigma influences resource allocation negatively.(Sartorius, 2007) Admission to a general hospital psychiatric unit may be less stigmatising than admission to a stand-alone psychiatric hospital.(Pillay & Kelly, 2009) Professionals and consumers need to be more proactive in educating the media.(Miller, 2007) The *Time to Change*⁵³⁷ initiative in Britain was launched in 2009 and aims to tackle stigma attached to mental illness.(Eaton, 2009; Henderson & Thornicroft, 2009) According to the Department of Health in the UK in 2009⁵³⁸ the public there are broadly sympathetic towards people with mental health problems. More attention needs to be paid to bolstering the self esteem of people with mental illness.(Thornicroft, 2009)

The lower socio-economic classes are more likely to be referred by the police and the courts, whereas physicians more often refer the upper classes (or the latter may self-refer). Attitudes towards and knowledge of treatment resources differ between social classes. Inner London boys (West, 1982) were more likely to be delinquent if they came from big or poor families, if there was poor parenting or marital disharmony, if the parents had criminal records during the boys' youth, or if they had below average intelligence. Women are far more likely to be killed by their present or former partners than are men.(Home Office, 1995) Associations of offending with physique, the old somatotype chestnut, are irrelevant when social factors are taken into consideration.

Stalkers are a heterogeneous group. About 8% of women and 2% of men experience unwanted contacts and intrusions that cause significant fear and apprehension.(Mullen ea, 2000) Doctors and health care professionals are at increased risk of being stalked, particularly by their patients.(McIvor & Petch, 2006) Stalkers who harass the British Royal Family are most likely (83.6%) to suffer from serious mental disorder.(James ea, 2009) Most stalkers are men, often unemployed, and relative to criminals in general, better educated.(Nadkarini & Grubin, 2000) Most victims are women. Female stalkers are equally likely to be violent as are male stalkers, they tend to stalk professional helpers more than strangers, and, unlike their male counterparts, they are more likely to target same gender victims.(Purcell ea, 2001) Homosexual victims may not receive needed help because of homophobia. Stalking activities include following a victim, communicating⁵³⁹, ordering goods or services for the victim, and aggression/violence⁵⁴⁰. Motivation arises from different forms of psychopathology, including psychosis and severe personality disorder.(Kamphuis & Emmelkamp, 2000) Prolonged stalking can have long-lasting deleterious effects on the victim, in the form of anxiety, depression, PTSD, and even consideration of suicide.(Purcell ea, 2005)

Based on an Australian study (Purcell ea, 2009) juvenile stalkers are mainly males and victims are female and previously known to the perpetrator and the stalkers directly approach the victim or use the telephone or send texts; assaults (physical and verbal) and threats are common; and stalking could be described in

⁵³⁷ Comic Relief and the National Lottery funded this campaign and the London Institute of Psychiatry undertook to evaluate its effects. Among the many approaches taken were prime time TV advertisements and beer mats stating that some of your co-workers probably have mental illness. Among the celebrities appearing in the campaign was the actor Stephen Fry. See www.time-to-change.org.uk.

⁵³⁸ 'Attitudes to Mental Illness 2009'.

⁵³⁹ Including on the Internet: cyberstalking.

⁵⁴⁰ According to McEwan ea (2009) previous violence is especially predictive of violence among stalkers, as are threats among ex-intimate stalkers.

terms of bullying, revenge for perceived harm, reaction to being rejected, and, in a small minority, sexual predation or infatuation.

Zona ea (1993) divided stalkers into simple obsessional (commonest; prior relationship with victim; violent), love obsessional (especially female; victim a male of higher social status; often psychotic; celebrity stalkers; no prior relationship), and erotomanic (deluded that victim loves them) groups.

Substance misuse increases the risk for violence. Psychosis requires treatment. SSRIs might help with intrusive thoughts. A co-operative approach, based on a risk-benefit assessment, by legal⁵⁴¹ and medical personnel is best.

According to Frude (1994), although early research suggested that marriage was better for men than for women, this has not been confirmed, and on average women benefit emotionally from marriage.⁵⁴² Women are more likely to acknowledge dependency needs than men if asked directly, but both sexes acknowledge such needs equally if the questions do not reveal their purpose, as in projective testing. (Millon & Davis, 2000, p. 13)

Loss of social attachments, such as job or spouse, increases vulnerability to mental breakdown. Downward social mobility is associated with a schizophrenic diagnosis. Migrants and minority ethnic groups have often been found to possess a high rate of psychiatric morbidity. This might have many causes, e.g. racism⁵⁴³, poverty⁵⁴⁴, (Brown ea, 1998) nutrition, housing, language problems, and different customs.

Schizophrenic patients tend to migrate to the anonymity of urban centres. Many migrant workers are illegal or badly treated by employers.

The premorbid characteristics (e.g. schizoid) of patients may militate against the development of social ties and supports. The elderly are given important roles in some societies and not in others, with consequent loss of self-esteem and material goods.

The availability of psychiatric institutions and treatment may explain differing hospitalisation and treatment rates more than do urban-rural or other variables. Diagnostic disparities, such as wide and narrow definitions of schizophrenia, are also important here. Some hospital personnel possess negative expectations for their patients that may have deleterious consequences. Psychiatry and other social institutions may be used by some people for manipulative reasons, e.g. to get a new house; ex-patients may simulate or exaggerate symptoms to regain admission.

*Non-compliance*⁵⁴⁵ with prescribed medication and other aspects of the therapeutic regimen is a major problem in psychiatry⁵⁴⁶ (O'Shea, 1995) as it is in other branches of medicine. (Powsner & Spitzer, 2003) Simon (2008), for example, states that 'sustained use of antidepressants is probably too rare to have much overall effect on risk of suicide in people living with depression.' Psychiatrists and patients may not always agree on the reasons for non-adherence. (Hoge ea, 1990; Haddad, 2008) Many patients stop treatment when

⁵⁴¹ In 1990, California passed the first antistalking law, making stalking a crime, the UK following in 1997. The Protection from Harassment Act 1997 in England states that psychological damage and the intent of the perpetrator must be demonstrated before a legal action can be pursued. Whilst the term 'stalking' is not used in the relevant Irish legislation, this activity is dealt with under Section 10 of the *Non-Fatal Offences Against the Person Act 1997* and conviction can attract a maximum of seven years in prison.

⁵⁴² However, Clare (2000, p. 82) suggests that for women, happiness within marriage is more important than it is for men!

⁵⁴³ African and Caribbean patients in the UK are overrepresented in UK psychiatric admission, involuntary admission, and duration of hospitalisation statistics. (McKenzie & Bhui, 2007)

⁵⁴⁴ Indian women show increased psychiatric morbidity if poor, married, smoke, have abnormal vaginal discharge, report a chronic physical illness, or have many psychological symptoms as baseline. (Patel ea, 2006) Numerous factors feed into mental health, e.g. poverty, disasters, war, aggressive recruitment of health workers by rich nations, education, etc. Poorer countries spend disproportionately less on mental illness than do wealthy nations. (Gureje & Jenkins, 2007)

⁵⁴⁵ *Non-adherence, non-concordance, non-cooperation.* Prof Elyn R Saks of California (2009), herself a law professor and patient on clozapine for schizophrenia, said 'part of the way I could prove that I was not mentally ill was to get off medication... (she then recounts her becoming psychotic)...all around me was evil beings...would slice me up...tell them not to kill me...all the explosions...I give life and I take it away (grandiose)'.
⁵⁴⁶ For example, up to 2 out of 3 patients with schizophrenia are non- or only partially-compliant with medication (O'Callaghan & McTigue, 1999), 50% of depressed patients stop treatment within 10 weeks, (Demyttenaere, 1997) people take lithium for a median of 72 days before stopping it without medical permission, (Scott, 2004) and over one-fifth of suicides were non-adherent to medication in the preceding month and nearly one-third had disengaged from services. (Swinson ea, 2007) The Clinical Antipsychotic trial of Intervention Effectiveness (CATIE: McEvoy ea, 2006) found that 74% of 333 (intent to treat) patients had stopped treatment within 4 months. Using pharmacy refill records, Dolder ea (2002) found that compliance was somewhat better for atypical (54.9%) than for typical (50.1%) antipsychotic drugs at 12 months, although not all studies would agree. (Gilmer ea, 2004) The Irish HSE reported almost 8 tonnes of medicines returned to 167 pharmacies in a 12-month period, 26.3% of which were classified as nervous system drugs that include psychotropics. (Culliton, 2008) Non-compliance is not confined to psychiatry, e.g. a patient who only takes thyroxine replacement therapy before bloods are due would show raised TSH as well as high T4 and T3.

they begin to improve. The stigma of being treated for an illness may discourage compliance.(O'Shea, 1995; Kemp ea, 1996) as may side effects or a feeling of not being in control.(Kemp & David, 1995) Sair ea (1998) classify barriers to compliance into medication related such as adverse effects, patient-related like unrealistic expectations, clinician-related such as ignoring patients' dissatisfaction, and organisational like an aversive clinic setting. At a much deeper level, some people cannot understand why disorders of an ephemeral 'mind' are treated physically, while others may see the necessity of such interventions as lowering humanity to the level of the common beast. Non-compliance in seriously ill patients, especially if combined with alcohol or substance abuse⁵⁴⁷, may be associated with violence.(Swartz ea, 1998) Cognitive dysfunction may be an important factor in decision-making capacity in the older schizophrenic.(Palmer ea, 2004) 'Compliance therapy', which involves going into a very detailed analysis of all possible issues with the patient, may improve adherence to prescribed treatments,(Kemp ea, 1996, 1998) as may involving patients in decision making (Britten, 1998) or primary care counselling.(Peveler ea, 1999) Motivational interviewing, assertive community care, precise instructions about what to take and when to take it, and intermittent reminders about the importance of adherence during follow-up may help.(Zygmunt ea, 2002) Not all research results find that compliance therapy is useful in schizophrenia.(O'Donnell, 2002, 2003) Bebbington and Kuipers,(2003, p. 618) having reviewed the literature, note that 'there was little evidence that effects of family therapy [in schizophrenia] might be mediated through improved compliance with medication'. Controversially, paying patients to take their medication has been suggested!(Giuffrida & Torgerson, 1997; Claassen ea, 2007; Burns & Shaw, 2007) Checks on compliance may be a two-edged sword, sometimes giving false reassurance.(Farragher, 1999) In fact, blood sampling is not a solution as patients are more likely to take their medication around the time of a clinic visit!(Cramer ea, 1990) However, serum levels of prescribed drugs may suggest poor compliance when all else (e.g. smoking) is considered, e.g. with clozapine.(Mennickent ea, 2010) Mutual respect between patient and prescriber is essential for treatment adherence (Shooter, 2003) and attitudes to treatment at baseline predicted adherence at one year.(O'Donnell, 2003) Many American states have strict laws requiring patients to comply with extramural treatment.(Rand & McKee, 1998) Attempts to introduce similar legislation on this side of the Atlantic have spawned considerable debate.(Burns, 1999; Moncrieff & Smyth, 1999)

Prisoners

Almost 9 million prisoners world-wide (Fazel & Danesh, 2002; Birmingham, 2004)

USA has highest imprisonment rate (686/100,000 pop. in prison in USA)

Men far outnumber women in prisons

Women tend to outnumber men in psychiatric care

Prisoners much more likely to be psychotic or suffer from major depression; 10 times more likely to have an antisocial personality disorder, than the general population (Fazel & Danesh, 2002)

Multiple incarceration is associated with psychosis and major mood disorders (Baillargeon ea, 2009)

Female gender and poverty⁵⁴⁸ strongly associated with common mental disorders (Patel ea, 1998) although the nature of relationship probably complex (Weich & Lewis, 1998; Sturm & Gresenz, 2002)

Factors associated with excess of prison suicides include psychiatric disorder (psychosis, depression, substance abuse) and ecology (bullying⁵⁴⁹, isolation, inactivity) (Casey, 2007)

⁵⁴⁷ Patients who believe (correctly) that one should not mix medication with alcohol or substances may decide to omit medication!(Brennan & Herman, 2008, p. 51)

⁵⁴⁸ 1.2 billion people around the world live on less than \$1/day. Even in Europe low socioeconomic status is associated with higher death rates and poorer subjective health, although smoking and alcohol contribute in part to such findings.(Mackenbach ea, 2008)

⁵⁴⁹ Kelleher ea (2008) found that 6.6% of interviewed North Dublin adolescents reported at least one psychotic experience and such symptoms were associated with childhood physical abuse, domestic violence exposure, and being a **bully** or being **bullied**. It is difficult to interpret such findings: pitfalls of interviewing, retrospection, direction of causation, and possible confounders (nature of vulnerability, poverty, drugs, etc). Schreier ea (2009) in England followed children and found that being a victim of bullying at 8 and/or 10 years of age increased the risk of psychotic symptoms two-fold at age 12 years and associations with peer victimization were stronger when victimization was chronic or severe, i.e. experience of relational and overt victimization. In a Finnish nationwide birth cohort study (Sourander ea, 2009) frequent childhood victimisation predicted later psychiatric problems irrespective of psychiatric problems at baseline, but frequent bully, victim, or bully-victim status did not predict and psychiatric problems among males, a finding that might possibly reflect methodological factors such as numbers or lack of sub-categorisation of bullying. Another

Female prisoner suicide standardised mortality rate (SMR) in England and Wales 1978-2004 was 20.7 (especially high in younger women) and SMR may be increasing (Fazel & Benning, 2009)
Prevalence (current, 6-month, and lifetime) of any psychotic disorder is more common in remand than in sentenced prisoners whereas the opposite seems true for major depression, especially lifetime prevalence (Curtin ea, 2009)

Response to treatment for depression may be retarded by poverty.(Cohen ea, 2006)
Being ill affects interpersonal relations, finance, jobs, accommodation, and so on. It may also symbolise failure to carry out ones social role. Patients and their relatives may go to great lengths to avoid consulting a psychiatrist because of stigma. This is particularly common in old age where dementia may be at an advanced stage before social breakdown forces referral. The discovery of mental illness in successive generations may be hushed up and rationalised, as often happens with Huntington's disease. Feelings of guilt in the relatives or disruption of a precarious social balance in the family may complicate the medical management of patients. Society condemns alcoholism and drug misuse and yet it also grants the same activities a certain prowess.
City life is generally associated with poor mental health in both children (Rutter, 1981) and adults,(Blazer ea, 1985; Weich ea, 2006) which may be a complex product of various factors including viral infections(Torrey, 1988) and childhood head trauma.(Field, 1976) Megacities in the third world with their rapidly expanding populations have been blamed for an expanding army of mentally ill people.(Klerman, 1976; Anonymous, 1997a) The role of housing⁵⁵⁰ in depression is complex, depending on who lives there, the social status of environs, and interactions between them.(Birtchnell, 1992) Mortality rates at all ages tend to be higher the lower the socio-economic status of the individual. Racial minorities in city centres may be at risk of not having their psychological problems identified.(Odell ea, 1997)

Irish in Britain

Reported to have very high level of service use, depression, alcoholism, schizophrenia, suicide and attempted suicide, admissions including involuntary admission rate, residence on secure wards, seclusion rates, referral from criminal justice
Described as mostly migrant workers, often unemployed, following employment, and homeless, and passing on their difficulties to the next generation (Bracken ea, 1998)
Walsh (1999; 2007) claimed that high British involuntary admission rates, older age (long-stay), low socio-economic status (more likely to be admitted) and out-of-date-data may account for these findings
Poorly planned migration blamed for depression in London Irish (Ryan ea, 2006)

Both long term (Scott, 1993) and temporary (Victor, 1992) homelessness are associated with an excess of mental disorder. The rising tide of homelessness may not be totally explicable on the basis of discharge from mental hospitals; other factors may include problems encountered in having mentally ill people admitted or readmitted to hospital (Lamb, 1993; Lamb, 1996) and the disappearance of affordable rented accommodation.(Leff, 1993) Homelessness does not appear to cause antisocial personality disorder, rather they have this profile before becoming homeless.(North ea, 1993) Caton ea (1994) found that drug abuse among seriously mentally ill men accounted for homelessness.

Dublin (Holohan, 2000)

29% of a homeless sample (only 64% of the known total of 780; 85% males) drank alcohol in excess of recommended limits, which compares favourably with general population (27% for males, 21% for females); majority of both homeless sexes were <45 years of age; 37% reported previous diagnosis of 2 psychiatric problems (32.5% depression, 27.6% anxiety) compared to 34% in a Sheffield (George ea, 1991) sample

Finnish study (Sourander ea, 2010) found that both cyberbullying and cybervictimisation are associated with psychiatric and psychosomatic problems.

⁵⁵⁰ Under the Irish *Housing (Miscellaneous Provisions) Act 2002* local authorities must provide housing to people in their area who require it.

Montreal (Roy ea, 2004)

Follow up of homeless aged 14-25 years; found standardised mortality ratio of 11.4; causes of death were suicide, overdose, unintentional injury, fulminant hepatitis A, and cardiac disease; predictors of mortality were HIV infection, alcohol use previous month, drug injection or homelessness in previous 6 months, and being male

San Diego County (Folsom ea, 2005)

Homelessness in patients treated for serious mental illness associated with male sex, being Black⁵⁵¹, substance misuse, lack of Medicaid, schizophrenia, bipolar disorder, and poor functioning

London (Abdul-Hamid ea, 2010)

Homeless men living in hostels require psychiatric and social assessments and alcohol and drug services; psychotic cases have high levels of unmet needs

Many psychiatric patients living rough fail to apply for their benefit entitlements.(Weller, 1989) Having been born in 1950s America, community psychiatry has arrived on the backs of a pharmaceutical revolution, hoped-for monetary savings,(Wildavsky, 1970) and the effects of social pressures born of an awareness of the poor condition of many Victorian institutions. Care in the community is universally hailed in principle but often condemned in practice. We are now in the era of bed shortages, high readmission rates, and revolving doors.(Appleby ea, 1993; Commander & Odell, 1998) Short inpatient stays in psychiatric hospitals are associated with high readmission rates.(Kammerling & O'Connor, 1993) Resettlement means moving patients from one place to another, such as from hospital to the community, whereas rehabilitation aims at minimising handicaps. Public hostility to community placement of mentally ill patients is quite common, at least initially, especially if placement is local and if adequate preparation of patients and the public is neglected. Some people have no objection to the 'insane' being deinstitutionalised as long as they are placed somewhere far from them, the NIMBY (not in my backyard) syndrome.(Sussman, 1997) Lamb (1996) was in favour of compulsory outpatient treatment and believed that Americans may be focusing excessively on liberty for patients 'at any costs'. Burns and Priebe (1999) warn that unless psychiatrists are proactive in advising governments about services we may be outvoted by more vocal groups whose proposals, whilst well meaning, may not be feasible or of practical utility. However, people usually want doctors when they are sick, but may avoid doctors when planning health care delivery.(Persaud, 2000) A novel idea is the use of negotiated joint crisis plans developed by patients and mental health staff that may include advance agreement on treatment preferences in case the patient later loses insight. There is some evidence that they may reduce involuntary admissions whilst not altering duration of hospital stay.(Henderson ea, 2004) However, Thomas and Cahill (2004) comment that 'the idea that we can soothe the pain of greater compulsion with the balm of advance statements is simplistic'. Patients' views about their involuntary admission (Priebe ea, 2010) varies with county studied, may become slightly more positive after a lapse of time, and may be more negative for females, people living alone, and if there is a diagnosis of schizophrenia.

See Change⁵⁵² (www.seechange.ie) was founded in Ireland in 2010 to tackle stigma associated with mental health problems.

Concern has been raised about direct advertising to consumer by the pharmaceutical industry⁵⁵³ aimed at the consumer and the potential for increasing costs⁵⁵⁴.(Bonaccorso & Sturchio, 2002; Gøtzsche, 2002; Mintzes 2002; Moynihan ea, 2002; Gilbody ea, 2004; Lenzer, 2005a,b; Anonymous, 2007a; Brown, 2007; Burton, 2008; Day, 2008; Dobson, 2008; Watson, 2009; Tanne, 2009a) Such direct advertising is currently prohibited in Europe but there is pressure to change this.(Moynihan, 2007; Toop & Mangin, 2007;

⁵⁵¹ Black Americans are relatively infrequent users of mental health services.(Neighbors ea, 2007)

⁵⁵² See Change works through the National Stigma Reduction Partnership, 38 Blessington Street, Dublin 7.

⁵⁵³ The most costly drugs to the Irish General Medical Services (GMS) scheme in 2002 were omeprazole (Losec), pravastatin (Lipostat), olanzapine (Zyprexa) – first to third respectively – and paroxetine (Seroxat), and risperidone (Risperdal) – ninth and tenth respectively.(Barry, 2002)

⁵⁵⁴ Drugs advertised in this way vary from antidepressants to drugs used for erectile dysfunction.(Rosenthal ea, 2002) Australia bans such practice and New Zealand was thinking of doing likewise in 2004.(Burton, 2004) Drugs may be portrayed in an unrealistically positive manner and doctors may be pressured to prescribe by patients and others.(Anonymous, 2005a; Kmietowicz, 2009) The US Congress has criticised drugs industry advertisements for overstating effectiveness and minimising risks.(Gottlieb, 2002) However, there are constitutional arguments favouring direct advertising (why not medication if alcohol can be advertised, etc?).(Shuchman, 2007)

Anonymous, 2008d, 2009; Watson, 2009) Whilst Canada also bans direct advertising of prescription drugs Canadians are influenced by TV and magazine advertisements from the US.(Mintzes, 2008) Doctors have become dependent on the pharmaceutical industry for funding research and declaration of interest may not always be forthcoming.(Editorial, 2002)

Informal carer stress⁵⁵⁵ (stress among relatives or friends who look after mentally ill people) is a newly recognised field for research. Women are the most common carers of sick relatives. Lauriello and Keith (1997) warn against families being asked to become the new 'back wards' of the community.⁵⁵⁶ Factors reported as being stressful include male sex of the patient, carers of high social class, difficult behaviour, negative symptoms, longer duration of illness, prior dependency on the ill person, and close relationship with the patient.(Olin ea, 1996; Tenakoon ea, 2000) Distress among carers can be persistent and may worsen over time.(Cooper ea, 2010) In a study conducted by Chessick ea (2009) increasing suicidal ideation had more negative subjective effects on the health of those caring for bipolar disorder patients than did static or declining suicidal ideation. Factors that were reported not to correlate with carer stress/distress include relationship of informant to patient.(Grad & Sainsbury, 1963; Mors ea, 1992) In a review of the literature, Fadden ea (1987) concluded that negative symptoms of mental illness, such as lack of conversation and non-performance of roles, are often a particular burden on relatives, that relatives do have a heavy burden to carry, that relatives complain very little and receive little support or advice, and that professional help has not improved much since the drive towards community care started. Indeed, voluntary befriending does not seem to help carers of people with dementia.(Charlesworth ea, 2008) Compared with control subjects, wounds in female carers of demented charges take longer to heal and their peripheral blood leucocytes produce significantly less interleukin-1beta mRNA in response to lipopolysaccharide stimulation.(Kiecolt-Glaser ea, 1995) Voluntary organisations tend to consider psychiatric interest in their endeavours in a poor light, although there much variation in this opinion.(O'Shea, 1989, 1992, 1994)

The UK Department of Health (2008) produced *Carers at the Heart of 21st-century Families and Communities* in which it was declared that carers would, by 2018, be respected as expert care partners and have access to integrated and personalised services to help them carry out their role; a life of their own alongside the carer role; have support to prevent being forced into financial hardship by the caring role; and have support to stay mentally and physically well and be treated with dignity. Children and young people will be protected from inappropriate caring and receive help to experience positive childhoods. Patient self-advocacy is a very late twentieth century phenomenon. Patient groups such as 'Survivors Speak Out' in the UK are expressing views on the kind of service that they want.

There are numerous self-help groups.⁵⁵⁷ 'Recovery', for example, was started by the psychiatrist Abraham A Low. It employs a cognitive system for managing temperamental behaviour and changing attitudes towards nervousness and fears. Recovery groups do not discuss diagnoses or treatments and insist on members co-operating with physicians. It is a useful adjunct to professional care, helping clients to cope between consultations and during aftercare.

A family may use the anger engendered by a chronic illness in a relative to found a support group or increase public awareness. They may become depressed, withdraw from one another, or engage in bickering among themselves. Elder abuse may be a symptom of carer stress.

We live in an ageing population.(Falvey & O'Shea, 1983) In 1991 and 1996 respectively, Ireland had 403,000 and 411,000 people over 65 years of age. One projection for the year 2026 gives a figure of 692,000. Put another way, 11.4% of people were at least 65 years old in 1996, the projection for 2031 being 18%. These figures make planning for the future an urgent necessity.

Euthanasia (mercy killing) is illegal in the USA but physician-assisted suicide is not illegal in Oregon (since 1997) and Washington⁵⁵⁸ states in the US, Switzerland, the Netherlands⁵⁵⁹ Belgium⁵⁶⁰ (Charatan,

⁵⁵⁵ The *Carers Act 2000* in the UK entitles carers to their own separate assessments.

⁵⁵⁶ Time spent looking after patients by carers would contravene the European Working Time Directive were it carried out by paid employees.(Doran ea, 2003)

⁵⁵⁷ See Anonymous(1997b) and telephone directory for Irish contact addresses and numbers.

⁵⁵⁸ *Initiative 1000* in the state of Washington legalised physician-assisted suicide in 2008. Votes for the legislation were 58% for and 42% against.(Steinbrook, 2008) State residents with less than 6 months to live must wait 15 days then request again in writing and by word; possible depression warrants mental health referral; 2 doctors must approve the request; and the patient has to administer the lethal drug (usually a barbiturate in Oregon) him/herself!(Dyer C, 2008) In both states (Washington and Oregon) the doctor can supply the prescription for the lethal dose of medication but he/she cannot administer it.

2000; O'Shea, 2004, 2005; Onwuteaka-Philipsen ea, 2005; O'Shea ea, 2009), and Luxembourg (from April 1, 2009) and, according to a Constitutional Court ruling in 1997, not illegal in Columbia, is the direct taking of a suffering individual's life by another person in order to reduce such suffering or avoid disability. The Australian Northwest Territory legalised euthanasia under the *Rights of the Terminally Ill Act 1995* but this was voided, after three deaths had occurred, by the *Commonwealth to the Northern Territory (Self-Government) Act 1978*. *Physician-assisted suicide* (PAS), long used synonymously with 'euthanasia' (*Lancet*, Feb. 25 1899, p. 532; Branthwaite, 2005; George ea, 2005; Sommerville, 2005; Tännsjö, 2005), is the indirect help given by a doctor to achieve death, as, for example, when supplying a lethal dose of tablets (incl. in neonates and infants: Feudtner, 2005; Provoost ea, 2005; Vrakking ea, 2005; Sheldon, 2005; Costeloe, 2007). It is legal in Oregon (Steinbrook, 2002) under its *Death With Dignity Act* (1994 & 1997), despite attempts by the US attorney general to outlaw it under US 1970 *Controlled Substances Act*⁵⁶¹. (Charatan, 2004) The *Death With Dignity Act* allows mentally competent terminally ill people (confirmed by 2 doctors) with less than six months to live to ask for a lethal dose of drugs. PAS accounts for about 1 in 1,000 deaths per year in Oregon, a frequency that remained fairly steady for the first nine years since the *Death With Dignity Act*. (Quill, 2007) The high court in Colombia⁵⁶² ruled in 1997 that euthanasia was not a criminal act if the person had a terminal illness, wanted to die, and no medical treatment existed, leading to a legal no-man's-land where the practice was not prohibited but wasn't entirely legal. (Ceaser, 2008) The ruling Socialist Party in Spain is considering paving the way for assisted suicide (Villaneuva, 2008a) and Spanish law was changed in 2010 to allow abortion on demand up to 14 weeks gestation (de Lago, 2010a) and without parental consent. However, appeals have lodged with the Spanish Constitutional Court. (de Lago, 2010b) Portugal's medical ethical code condemned both abortion⁵⁶³ and euthanasia but, since 2008, it simply demands respect for life from the time of conception. (Villaneuva, 2008b)

Some doctors practice euthanasia/ physician-assisted suicide (E/PAS) in some form or other outside the law, (Mitchell & Owens, 2003; van der Heide ea, 2003; Turone, 2007; Dyer O, 2008) and not necessarily accompanied by an explicit patient request. (van der Heide ea, 2004, 2007) Courts have accepted testimony of third parties that it was a person's wish to die⁵⁶⁴. (Grayling, 2005) In November 2001, the British House of Lords refused a woman⁵⁶⁵ with motor neurone disease the right to choose her time of death and stated that her partner could be held legally accountable should he assist in achieving her demise.⁵⁶⁶ The English High Court granted a woman with cerebral ataxia the right to travel to Switzerland⁵⁶⁷ in 2004 where she terminated her life. In 2009, the Swiss government considered new laws to make it harder for foreigners to travel to Swiss clinics to get assistance to end their lives⁵⁶⁸. In 2004, the French National Assembly passed a law allowing conscious, terminally ill patients to refuse life-prolonging treatment. In 2007 Dr Laurence

⁵⁵⁹ The Dutch *Burial Act* was amended in 1993 to permit assisted suicide. The Dutch Foundation for Scientific Research into Careful Suicide provides advice on suicide at www.wozz.nl.

⁵⁶⁰ Belgian law acknowledges that mental suffering is a valid ground for euthanasia. (Naudts ea, 2006) Interestingly, Belgium legalised euthanasia despite having a very well developed palliative care system. (Bernheim ea, 2008)

⁵⁶¹ In *Gonzales v. Oregon* (2006), the US Supreme Court held that the US Attorney General could not use the *Controlled Substances Act* to stop Oregon doctors prescribing regulated drugs for use in PAS. The US Supreme Court (*Cruzan v. Director, Missouri Department of Health*, 1990) had previously held that the dying could refuse life-sustaining interventions.

⁵⁶² 95% Catholic population.

⁵⁶³ A referendum of 2007 led to abortion being allowed in registered centres up to tenth week of pregnancy. The ethical code only allows abortion if it is essential in order to save the mother's life.

⁵⁶⁴ In 2005, the Terri Schiavo case in Florida (brain damaged woman on life support) created great controversy.

⁵⁶⁵ Diane Pretty (d. 2002). In 2008, Debbie Purdy, a British woman with multiple sclerosis, won the right for a judicial review of whether her husband (Cuban violinist Omar Puente) would be held accountable if he brought her to Switzerland for PAS. The High Court refused her application and stated that only Parliament could change the law. In the same year, Daniel James (23, rugby injury, tetraplegia) was accompanied by his parents to Zurich for PAS but the director of public prosecutions (DPP) in England decided not to prosecute the parents because it would not be in the public interest. In 2009, Debbie Purdy (MS) received unanimous backing from the Lords for a policy statement from the DPP. The English DPP published guidance in early 2010 (Coggon, 2010) and listed factors for (e.g. victim < 18 years, lack of victim capacity, victim under doctor's care) and against (e.g. tried to dissuade victim or gave only minor encouragement) prosecuting with special relevance to medical personnel. In 2010 Tony Nicklinson (56) in the UK, a sufferer from locked-in syndrome following a stroke, asked the DPP (via his solicitors) if those carrying out mercy killing/voluntary euthanasia would be prosecuted.

⁵⁶⁶ The European Court of Human Rights upheld this refusal in 2002.

⁵⁶⁷ Zurich clinic run by *Dignitas* (founded 1998 by journalist and lawyer Ludwig Minelli).

⁵⁶⁸ The British conductor Sir Edward Downes (no terminal illness, aged 85) and his wife (Joan, had terminal illness) used *Dignitas* services in 2009.

Tramois of France received a one-year suspended sentence for a 2003 killing of a cancer patient.(Mullins, 2007) Under English law (*Suicide Act 1961*) assisted suicide carries a maximum prison sentence of 14 years⁵⁶⁹.(Huxtable, 2004; Dyer, 2007a) Whilst, at the beginning of 2005, the English Courts empathised sufficiently with the male survivor of a marital suicide pact to hand down a short suspended sentence, the UK House of Lords rejected a bill to legalise PAS in May 2006.(Dyer, 2006) In January 2007,(Dyer, 2007b) England's senior family judge ruled that life sustaining treatment could be withdrawn from a woman in a persistent vegetative state following brain haemorrhage. The conviction of Nicholas Reed, the former secretary of EXIT, for assisted suicide led that group to change its name to the Voluntary Euthanasia Society. Since 2000, Dutch law holds that only a medical doctor can consider a request for PAS and such request must stem from a physical or mental disorder, not an 'existential' (i.e. in the absence of a physical or mental disorder) source.(de Vries, 2003) A problem arises when a patient wants to die but the (Dutch) physician does not think that the patient's suffering is 'unbearable'!(Pasman ea, 2009) Onwuteaka-Philipsen ea (2003) found that the demand for PAS had not risen among Dutch physicians and patients since 1995; the authors deduced that the Dutch 'seem to have become somewhat more reluctant in their attitude towards this practice'. In fact, euthanasia and PAS declined modestly from 2001-5, perhaps replaced by other options such as 'palliative sedation'⁵⁷⁰.(van der Heide ea, 2007; Mullins, 2008; Rietjens ea, 2008) Dutch physicians usually refuse requests for PAS in the absence of severe disease, but most patients persist in their request.(Rurup ea, 2005) Dutch medical mercy killing of severely ill newborn babies does not seem to have become common, probably this is because of abortion, fear of litigation, and lack of knowledge of what is involved.(Sheldon, 2009) According to Swarte ea,(2003) the Dutch experience with cancer deaths is that the bereaved seem to cope better if death is due to euthanasia than if it occurs naturally. Advising a patient on the lethal dose of a drug does not appear to be illegal in the Netherlands.(Sheldon, 2007) Pain as a reason for requests for PAS to have decreased, probably because of improved pain management, to be replaced by deteriorating health and increased emphasis on 'self-esteem'.(Marquet ea, 2003) Hendin (1997) suggests that Dutch patients are subtly coerced by relatives and enthusiastic doctors to accept euthanasia. Switzerland has very liberal laws on assisted suicide: patients must persistently want to die, be of sound mind, have an incurable disease, and carry out the final act themselves. Technically, PAS is illegal in Switzerland, but to be guilty of an offence it must be shown that one acted selfishly⁵⁷¹.(Ziegler & Bosshard, 2007) Guidelines for PAS are now commonplace in Swiss hospitals.(Tuffs, 2007a) Prescribed barbiturates are the usual method in Swiss PAS. Lausanne University Hospital decided in 2006 to allow assisted suicide groups onto their premises to help terminally ill patients die.(Chapman, 2006) The wish to die is subject to great variation over time, and is influenced by many factors, especially depression.(Chochinov ea, 1995; Breitbart ea, 2000; O'Shea 2000a,b; Schuster, 2000; Blank ea, 2001; Kelly ea, 2003; Barnow ea, 2004; Marcoux ea, 2005; Ganzini ea, 2008; van der Lee, 2008) Depressed patients are more likely to refuse cardiopulmonary resuscitation (CPR).(Lifton & Kett, 2000) Fourteen percent of terminally ill cancer patients in various settings were found by Kelly ea (2003) to wish to hasten death and this wish was associated with depressive symptoms, hospice inpatient status, seeing oneself as a burden, low family cohesion/social support, high anxiety levels, and greater impact of physical symptoms. Hospice nurses and social workers in Oregon have viewed the chief reason for a request for PAS differently, placing a need to control the circumstances of death way ahead of depression, lack of social support, and fear of being a financial drain on the family.(Ganzini ea, 2002) States intending to legitimise PAS would do well to look first to the care already given to the dying (Ganzini & Block, 2002; Swarte ea, 2003) and the reasons why some people want it.(Mak ea, 2003) Peretti-Watel ea,(2003) reporting on a telephone survey in France, found that GPs and neurologists more than oncologists wanted euthanasia to be legalised; the authors suggested that a lack of knowledge about palliative care might explain this finding. Van den Block ea (2009) found that end of life decisions (including euthanasia/PAS) as reported by GPs in Belgium are not a reflection of lower resort to palliative care but 'often' (but see

⁵⁶⁹ The BMA in Britain has a tendency to swing to and fro on the issue.(Kmietowicz, 2006)

⁵⁷⁰ This term may be misleading as some authors contrast *palliative* (without the aim being death even if death occurs as a side-effect) with *terminal* (knowing the patient will die shortly) sedation.(Murray ea, 2008) In the Rietjens ea (2008) study, a nationwide questionnaire-based study of physicians, such continuous deep sedation increased from 5.6% to 7.1% of deaths between 2001 and 2005. Benzodiazepines were used in 83% of cases. 94% were sedated for > 1 week prior to death. 9% of those receiving sedation had unsuccessfully requested euthanasia. 9% of physicians had consulted an expert in palliative care. Cunningham (2008) has discussed the ethical use of sedation in the distressed dying.

⁵⁷¹ Article 115 of Swiss Penal Code.

Byock, 2009) occur in the context of multidisciplinary care. This study did not access hospital personnel and could not measure cause and effect. Blass and Ratan (2003) express worries about precipitating requests for PAS in patients by telling them that they have incipient Alzheimer's disease based on neuroimaging findings. In 2005, the Dutch euthanasia assessment committee reported that a doctor lawfully complied with a request for euthanasia from a patient with Alzheimer's disease. In fact, only 4 of 1886 cases of euthanasia/PAS in 2004 failed the Dutch legal requirements. The law requires that such cases be referred to the public prosecution service.

Palliation⁵⁷² is well within the Hippocratic tradition even though whilst it doesn't try to hasten death it doesn't seek to prevent it ('passive euthanasia'). (John Paul II, 1995; Keown, 2002) The ethical practitioner does not need to go to extraordinary lengths to preserve life but he/she should strive to minimise suffering. Beyond the death of the individual person and its immediate legal/moral implications, the major problem with active euthanasia is that its social acceptance removes any 'principled objection' to involuntary euthanasia. (Hughes & Baldwin, 2008, p. 726) The belief that all cases receiving PAS were 'terminal' may not be correct. (Koch, 2008) There is pressure in the Netherlands from *Uit Vrije Wil* (Of One's Own Free Will) to allow PAS for older people who are not dying but that feel their life is complete. (Sheldon, 2010) Also, not all dying people are free of fear. Dying people are vulnerable and are potentially open to exploitation. (Carlile, 2009) The increasing technological approach to medical practice should not divert practitioners from recognition of the fact that a person is dying and requires palliation and Livesley (2010) suggests that this has compromised our caring role to the extent that those who advocate assisted dying end up looking like the only people who care.

The relation between *religion* and risk for depression is complex and simple explanations may be misleading. (Maselko et al., 2009) Psychiatrists may be hostile to religion⁵⁷³ as a group (Dein et al., 2010), a

⁵⁷² A postal survey of UK medical practitioners (Seale, 2009) found that only 9% of doctors believed that they should be able to end the lives of people who had incurable and painful disorders compared to half of the general public who favoured physician-assisted death. The strongest opposition came from specialists in palliative care, followed by those charged with looking after the elderly.

⁵⁷³ *Religion* refers to socially based beliefs/traditions with/without ritual/ceremony. *Spirituality* is a strong sense of connection that enables a person to feel that his/her life contributes to a greater and valued whole, that we are not meaningless within the Universe. (Dein et al., 2010) Serious illness and death of a valued other may generate a crisis of meaning. A few notes on various **religions** in relation to healthcare issues will be made here (Mootoo, 2005; HSE, 2009). People who do not have religious beliefs may describe themselves as such or as humanist, agnostic or atheist. In-patients with this status should not be made to feel embarrassed during hospital-based religious services. Non-religious funeral ceremonies can be organised by the Humanist Association of Ireland (www.humanism.ie). Religious symbols (e.g. a plain cross in the case of Anglicans) should only be removed when essential (e.g. radiological study or cleaning the deceased) and should be replaced as soon as possible. Many religious and cultural groups have their own herbal remedies (which may interact with orthodox prescriptions) and washing rituals. Where medicines contain animal products forbidden by a particular religion the adherent will want to decide on whether to take them or not. Traditions requiring candles to be lit near the deceased should be accommodated if it is safe to do so. Those traditions mandating multiple visitors to the sickroom may be requested to rotate visitors or may be asked to leave a few visitors with the patient while others pray in a prayer room. Coroners should be advised where religion mandates early burial so that a Death Certificate is not unduly delayed. Some traditions have beliefs that may clash with those of the majority of the population but they must nevertheless be respected, e.g. some African Pentecostals may explain illness as being caused by unseen agencies and they may request that their pastor pray to God to intervene (although this does not normally cause problems with the simultaneous acceptance of medical intervention). There is some degree of pastoral cross-cover among the major non-Catholic Christian traditions but this will require clarification in each case. The tradition of the *Irish Traveller Community* (who are mostly Roman Catholic) held that pregnant women should avoid dead bodies and this practice may still pertain. The *Roma* (Lit. 'people') community may speak a Romani (this is nothing to do with Romanian) dialect and most members are Pentecostals with some being Roman Catholic or Orthodox Christians. Some traditional Roma women may want their menfolk to talk on their behalf but this cannot be assumed. The Roma often visit the sick in large numbers and they usually want to bring a deceased member's remains home as quickly as possible where the body will be displayed for two nights. Bereaved Roma wear black for one year and the men do not shave during this time. (**Roman**) **Catholics** will want a priest in attendance if a patient is close to death and newborn children who are dying should be baptised (by a Christian layperson if clergy are unavailable); the *Sacrament of the Anointing of the Sick* may be given to ill people or those facing major surgery and the *Viaticum* is given to those close to death. A dead infant cannot be baptised but can be named. Some Catholics are buried in a shroud. Baptism in the **Orthodox Church** is normally conducted when the baby is 40 days old, unless the baby is dying in which case the Orthodox priest or the parents can conduct the rite. Orthodox Christians believe that the deceased should be buried whole and undamaged. Sacred icons are an important part of the Orthodox tradition. In an emergency, **Church of Ireland** (*Anglican* or, in Scotland or US, *Episcopalian*) lay people can baptise an infant or child. **Baptists** do not baptise infants even when death is imminent; a minister of that faith may perform a *Naming Ceremony* if the child dies (including miscarriage/stillbirth) before it can be baptised. They may however hold a dedication service. **Lutherans** baptise during infancy and any Christian can perform this ritual in an emergency; a blessing may be offered in the case of miscarriage. **Methodists** do not have a formal death rite but they usually want a dying baby to be baptised. **Presbyterians** may want a minister of their faith to be called in cases of death in order to help them pray but the dead, including a child, are deemed to be in God's hands so a chaplain need not be called after death as such; non-ordained adherents may pray for and name a deceased newborn child but they cannot baptise the baby. **Pentecostals** (belonging to many different Churches) receive

phenomenon dated to Charcot and Freud.(Koenig, 2008) We must take our patients' religious and spiritual beliefs into account more than we have in the past.(Cook, 2010; King & Leavey, 2010) We may avoid doing so because we believe that religion is irrelevant generally or to psychiatry in particular, we do not see ourselves as theologians, or because we are fearful of such matters.(Sims, 1994; McClain ea, 2003) Religious patients may have difficulty confiding in a psychiatrist who they perceive as unbelievers or as disparaging of religion.(Dein ea, 2010) There are instances where involvement of a pastoral counsellor is relevant, where supporting religious belief is important, and, when we know our patients well, when confronting unhelpful beliefs may be indicated.(Koenig, 2008)

Sociobiology is the study of the biological basis of social behaviour. It integrates principles of evolution, genetics, ecology, and ethology. Important concepts in sociobiology include the following: *Fitness*, the highest measure of evolutionary success has been reached in that the best genes are passed down through the

baptism when an adherent is ready to receive this sacrament and infant baptism is not a requirement of this tradition. The **Religious Society of Friends** ('*Friends*', *Quakers*) have no clergy but may want a visit from a fellow adherent such as an elder during times of distress; baptism is not necessary for infants who are dying; funerals are silent apart from acknowledging manifestations of God's goodness in the deceased and requests for comfort for the bereaved. **Seventh-day Adventists**, who have the same Sabbath as do Jews, must not eat 'unclean' food. They may be vegetarians or vegans. Alcohol, including during *Holy Communion* (pure grape juice is allowed), is avoided. Baptism by full immersion only takes place when the 'age of accountability' is reached. **Church of Jesus Christ of Latter-day Saints** should be referred to as *Latter-day Saints* rather than as *Mormons*; *home teachers* visit their sick and *elders* perform religious ceremonies; blessing of the sick involves anointing with oil and laying on of hands; burial is preferred to cremation; and baptisms (normally conducted at age 8 years) of infants who are dying is not deemed to be necessary. **Jehovah's Witnesses** have Hospital Liaison Committees that provide support, mediation, and information when medical interventions are proposed; blood, blood cells and plasma (including in foods such as black pudding) are not allowed (adherents vary in relation to use of the patient's own blood or the use of albumin, clotting factors and immunoglobulins; organ donation/transplantation is based on personal choice); baptism of the newborn is not practiced (baptism occurs when the person understands its implications). **First Church of Christ, Scientist** (*Christian Science*) adherents may only be in hospital for childbirth, following an accident or secondary to family pressure and members should be allowed to discuss the level of care they will accept (children can be treated in accordance with State Law); a time to pray may be requested before a medical intervention; females should handle deceased female Christian Scientists; post-mortem examination requires compelling reasons; cremation is more common than burial; and baptism is not part of Christian Scientist ritual. **Bahá'í** adherents customarily put a ring on the finger of the deceased and this should never be removed. The Bahá'í forbid cremation and insist that the deceased is interred as near as possible to the place of death. **Judaism** (*Jews*) mandates dietary rules (*kosher*). The advice of a rabbi may be sought when major life questions arise. The Jewish Burial Society (*Chevre Kadish*: not available during *Sabbath*, i.e. sunset on Friday to nightfall on Saturday) will prepare the deceased, and the body, unwashed by healthcare workers and with tubes and dressings in place, should be left in the mortuary until the community arrives; mementos (e.g. a lock of hair) are not to be removed from the body; relatives may request that the body of the deceased be placed on the floor with feet pointing to the door and a window left open; burial (never cremation) is carried out as soon as possible after death and post-mortem examination should only be conducted if the law requires it; traditional mourning lasts for 7 days; and foetal losses after 3 months of pregnancy are given full Jewish ritual. Orthodox Jews do not use electrical appliances such as telephones on the Sabbath; neither do they travel during that period so visitors may need assistance with somewhere to rest; and women may want to light candles at the onset of Sabbath. Males over 13 years of age may wish to pray wearing religious garments such as a shawl. **Islam** (*Muslims*) is divided into the Sunni and Shi'a traditions; the left hand should where possible be left free for washing; when a child is born the parent, usually the father, recites a prayer into each ear in turn; patients should eat *halal* food (pork and alcohol are forbidden); during *Ramadan* food and liquid are avoided from dawn to dusk, although pregnant women, the ill and children are not subject to this rule; just before death the person should be turned toward Mecca; the body of the deceased should not be washed by healthcare staff and touching the body is a task for same-sexed staff; the dead, who should be modestly covered, are believed to retain awareness; essential post-mortems should end with restoration of removed organs; full ritual is carried out after death for foetuses that have developed; burial (in shroud and facing Mecca; cremation is forbidden) should be as soon as possible. **Hinduism** (*Hindus*) is often associated with *Ayurveda*, a traditional medical system involving herbs, exercise and diet. Beef (sometimes pork) and its derivatives are disallowed (if these are in prescription medicines the patient has a choice to make). Babies are blessed and named on the tenth day of life. Intra-uterine death from the third month onwards is treated as for infants. Family and/or husband involvement in decision making is very common. If family are not available then healthcare staff can clean and wash deceased Hindu adherents; a lighted candle is left near the head of the body; and cremation takes place within 24 hours of death with the ashes then scattered into a river, followed by 13 days of mourning. **Sikhs** have strict dietary practices and will want to know if medicines contain proscribed agents such as alcohol. They have a strict dress code (including a strapped miniature sword and a turban – when necessary for examination or treatment purposes, patients should be asked to remove their own turban). Deceased members should be washed by same-sex healthcare workers. A dead child should be wrapped in a clean white cloth before being handed over to the family. Do not remove a lock of hair as a memento for the family. If one has to cut hair then consent should be sought when possible. **Buddhists** believe that consciousness is retained for about 4 hours after death and they wish for a peaceful and private environment, unaffected by mind-altering medication, during their last hours so that the spirit (i.e. consciousness) can gently exit the body through the top of the head (sometimes assisted by tapping the head). The body should not be laid out for at least 4 hours, the head should remain untouched, and only essential cleaning (e.g. blood) should be undertaken by staff. Sacred symbols (*Prayer Mandalas*) may be placed on the deceased and these should be left *in situ*. Post-mortem examination should be delayed for a minimum of 4 hours and preferably for some days. Finally, some people practice ancient/traditional religions such **Druidry** and **Shamanism**. Patients should be asked if there are particular requirements in the context of medical treatment or if there are any observances in relation to death or dying, e.g. some women may want to bring the placenta home in order to dispose of it according to their particular belief system.

generations. *Inclusive fitness* is the sum of an individual fitness plus that of his relatives compared to the rest of the population. *Resource holding potential* (RHP) is an animal's ability to defend a disputed territory or resource, the greater the RHP the more successful is the animal. *Sexual dimorphism* means that female and male behaviour evolve differently to ensure maintenance of resources and reproduction. Finally, *altruism* is overtly unselfish behaviour that is really genetically selfish because it allows survival by another member of the population.

*Internet*⁵⁷⁴ *addiction* (Murali & George, 2007) affects a minority of users of the internet. It can be defined as excessive, maladaptive, or addictive use of the internet. There are many possible causes, e.g. operant conditioning, immediate reward, impulsivity, shyness, and introversion. This controversial 'entity' has a broad comorbidity ranging from ADHD to shyness. The excessive user may focus on cybersex, gambling, shopping⁵⁷⁵, database searching, or games. Adverse effects include reduced time spent in real-life relationships ('cyberwidow'), poor academic/occupational performance, loneliness/frustration/depression/suicidal ideation (Fu ea, 2010), and fatigue. Approaches to treatment include behavioural strategies (e.g. outdoor activities), support groups, and cognitive therapy.

Systems Theory

Everything is made up of a hierarchy of concrete systems that are made up of matter and energy. The parts of a system are interdependent and interact in the system. At a very low level of the hierarchy are atoms that contain sub-atomic particles. Further up the line are cells. Further up again are multicellular organisms, such as man. Beyond this are flocks of sheep, families of humans, armies, nations, international groups, et cetera.

External systems interact with any given system. Systems can be living or inanimate, and each has evolved methods of communication between its components and tended to become more complex over time.

Adaptation to external stresses and demands led to specialisation within organisms⁵⁷⁶.

Humans developed a capacity for symbolic language.(see box) Group efforts allow us to produce objects beyond the capacity of individual organisms, e.g. cities, hospitals, rockets, and the delivery of the mail.

Despite this level of sophistication, we still can only survive within very narrow limits of, for example, temperature or acidity.

Systems contain subsystems that carry out certain processes, e.g. heart muscle, excretion, and so on.

Suprasystems are above the system; e.g. the individual person belongs to his family. Reproduction allows the continuance of the type to which a system belongs. Homeostasis allows the human system to survive despite fluctuations in the external or internal environments. If such changes prove extreme the system is strained. Excessive strain leads to pathological change. Systems have in-built positive and negative feedback mechanisms to enable fine adjustments to be made, e.g. the output of thyroid hormones.

Language

Discourse analysis: that aspect of pragmatics seeking to establish why texts are coherent

Linguistics: refers to the systematic and objective study of language

Metaphonology: rules governing permitted phonemic combination and subtleties of pronunciation

Phoneme: constituent speech sounds

Phonological receptivity: an ability that is at its height during infancy and fades until before adolescence; deterioration in this ability makes learning a new language difficult after the early childhood years

Phonology: study of sound patterns morphology and syntax, study of word and sentence structure

Pragmatics: use of language for interpersonal communication; use of language in natural settings, i.e. conversation; tone may be employed to convey feeling; familiarity with the listener or the context of the discussion leads to variation in what is said and how it is said

Prosody: rhythm and melody of speech

Psycholinguistics: studies the relationship between language and mind; must be taken into account in cross-cultural studies

⁵⁷⁴ See Perecherla (2009) for an introduction to internet matters, including 'telepsychiatry' (provision of services to remote areas).

⁵⁷⁵ DSM-IV-TR impulse-control disorders not otherwise specified include pathological shopping or spending, compulsive sexual behaviour or face-picking, and repetitive self-mutilation. **Compulsive or pathological shopping** (*mall mania*) may share some characteristics with substance use disorders, OCD, affective disorders, or anxiety.

⁵⁷⁶ E.g. some cells became able to contract very well, others to secrete specific substances in large quantities, and others to carry messages.

Semantics: study of meaning

Sociolinguistics: relationship between language and social groups

Syntax: grammar and word order, i.e. language rules on how to combine words to produce phrases/sentences

Information processing within the human system is highly complex and subject to pathological change in various ways. Psychoanalysts recognised that the psyche contained a number of homeostatic mechanisms, known as defence mechanisms, which guard against overwhelming anxiety or psychosis.

Group dynamics can be understood in terms of systems theory. In order to understand why something is happening to a person we must understand the system(s) within which he exists, the suprasystems(s), the subsystems, and the interplay of information to and from that person and all of the above. (Lipowski, 1975; Browne, 1988).

According to systems theory, intrafamilial interactions are multidirectional, homeostasis is desired and threatened by change, and scapegoating may be used to regain equilibrium, the scapegoat being presented as the 'patient'. The family therapist focuses on family interactions (e.g. communication patterns, unspoken rules and games, authority structure) and attempts to alter these.

Minuchin developed *structural therapy*. The family consists of a hierarchy of subsystems (spouses, parents, and siblings) with clear but semipermeable boundaries between them. Dysfunction may occur because of excessively rigid (*disengagement*) or diffuse (*enmeshment*) boundaries. Disruption may be due to overprotection, rigid behaviour, poor conflict resolution, or the involvement of offspring in marital conflict. Therapy aims to restructure appropriate subsystems.

Crisis Theory and Therapy

A crisis is a response to a hazardous event and is experienced as a painful state. If reactions are appropriate, then normal functioning resumes. The person learns more about adaptation because of the experience, and psychological growth may follow. Maladaptive reactions make matters worse and can cause psychiatric symptoms leading to neurotic behavior and poor function. Responses may be extreme, even including suicide.

In a crisis the anxiety level rises leading to attempts to solve the problem. The outcome depends on the effectiveness of the response. The person devotes all his energy into resolving the present crisis. He may seek outside assistance. Hopefully, he learns how to foretell, resolve or prevent such events in the future. The therapist, when faced with a patient of limited resources, aims at shoring up existing defences using supportive measures. In the case of people who are basically sound, but who from time to time experience neurotic breakdowns, and who are able to handle anxiety, he may indulge in dynamic psychotherapies which tend to provoke further anxiety. Supportive techniques include explanation, reassurance, advice, medication, environmental manipulation, and, if necessary, brief periods in hospital. Brief psychotherapy may be conducted in individual (therapist and patient only) or group (e.g. couple, family, large groups) settings. Anxiety-provoking techniques are only suitable for those clients who are highly motivated to understand themselves better and who are highly desirous of change. In dynamic therapies the therapist focuses on the crisis itself, the client works actively with the therapist in a therapeutic alliance, transference reactions are made use of (ignored in supportive cases), and the hope is that this turns out to be a true learning experience. Sifneos (1979) discusses short-term dynamic psychotherapy

Concepts or models of Disease⁵⁷⁷

How can we capture the essence of disease when health, often defined by the absence of disease, is itself difficult to put into words? Psychiatric disorders are symptom-dependent and the symptoms themselves are hard to describe. (McKenna, 2007, p. 81) What is regarded as illness, including a legitimate illness, may vary with time and the prevailing predominant culture. (Shorter, 1995; McCabe & Priebe, 2004) It may also vary with governmental policy, e.g. the UK government's 1999 declaration that it intended to introduce legislation for the 'compulsory and potentially indefinite' detention of persons with 'dangerous severe personality disorder'. This rejuvenated the debate as to whether the personality disordered were ill *per*

⁵⁷⁷ According to Jager (1999), 'Prostitutes and lawyers may have clients. Psychiatrists have patients'.

se.(Kendell, 2002) *Drapetomania* referred to an 'excessive' desire on the part of Negro slaves in pre-Civil War America to escape!(Brown ea, 1998)

According to Kreitman (1989), the essential task for both the clinical psychiatrist and the researcher is to 'understand how social, somatic, and psychological processes interact and how they sometimes lead to feelings of distress...a secondary distinction may then be drawn identifying those types of distress that are appropriate for the medical profession, broadly defined, and those that are not.'

Some criticisms of the notion of 'psychiatric disease'

Thomas Szasz (1960) - it does not exist

Franco Basaglia (1970) - an expediency suiting the ruling authorities

R. Leifer (1971) - an ideology

Scheff and others – we are simply labelling people

Labelling (see Gould, 2005) may lead to 'secondary deviance', promoting or reinforcing socially deviant behaviour. Depending on the onlookers' viewpoint, the constant alterations in, and dissatisfaction with, current psychiatric classification may be viewed as evidence of ignorance or as a quest for better understanding.

Alternative 'explanations' for psychiatric problems include badness, social problems, clashes of personality, demonical forces, learning problems (neurological or inadequate or unhealthy role models or experiences), separation experiences at vulnerable developmental stages, communication problems, deficits in inferential reasoning,(Charlton, 1995, who advocates a computer model of the mind) low self-esteem, fixed patterns of attribution, genetic traits, acquired biological damage, or a mixed bio-psycho-social diathesis.(George Engel⁵⁷⁸, 1982) At one time, mental functions were thought to be localised in the same manner as motor and sensory functions; at other times a holistic view held sway, the brain being seen as an 'equipotential diffuse organ'.(Berrios, 1991)

Illness and related terms

Patient: Lat. *pati*, to suffer; *client*: Lat. *clinare*, to learn.

Illness refers to feeling or looking unwell⁵⁷⁹. *Disease* is more difficult to define. The Concise Oxford Dictionary is unhelpful, defining disease as an 'unhealthy' state of the body, mind, or part thereof.

Traditionally in medicine, when a cause is known the term disease is substituted for other labels. However, Minas and Silove (2007, p. 512) are correct when they say that while organ systems may suffer disease it is 'only a whole, sentient person' who can be ill. A *syndrome* refers to a collection of symptoms and/or signs that occur together with sufficient frequency to suggest shared aetiological or pathogenic roots; even when causes are thought to be multiple it is assumed that they act through a 'final common pathway'.

Schizophrenia and ischaemic heart disease (IHD) are complex (non-Mendelian) disorders that arise from the interaction of a number of factors; we know more about the pathogenesis (mechanisms) of the latter than we do of the former.

ICD 10 tries to avoid the terms disease and illness, opting for the inexact word 'disorder' to imply the presence of 'a clinically recognisable set of symptoms or behaviour associated in most cases with distress and with interference with personal functions'. It states that 'social deviance or conflict alone, without personal dysfunction, should not be included in mental disorder' as defined in ICD 10.

Scadding's (1967) *biological disadvantage* concept of disease may be qualified by saying that, in certain circumstances, the individual's disadvantage (e.g. sickle cell anaemia) carries advantages for the wider group (who carry the gene for sickle cell anaemia and are protected against malaria).

Foulds' hierarchy, after Graham Foulds, a psychologist, who described it (Fould, 1976), places neuroses and personality disorders at the base of a pyramid. At progressively higher levels we find anxiety, depression, schizophrenia, and dementia. Disorders at a given level can have features of all the disorders

⁵⁷⁸ George L Engel (1913-1999) at Rochester, New York State.

⁵⁷⁹ Marshall & Klein (2002) define illness as being involuntary, with obvious effects on function and well-being, resistant to self-instruction, and persistence despite clear negative implications for the sufferer.

below it but not of those above it. Once popular, this diagnostic approach and explanatory paradigm has been largely displaced by an era of multiple diagnoses, i.e. co-morbidity⁵⁸⁰. Not everyone agrees with its displacement.

Diagnoses are often critiqued as being over-simplifications of real dilemmas, mixtures of other diagnoses, pejorative (e.g. hysteria), and conveying a false sense of understanding of a 'condition'. Diagnoses are concepts whose usefulness may (and have been) replaced by other concepts. They do, however, describe real phenomena, with the possible exception of some esoterica such as 'multiple personality disorder'. The DSM system of classifying mental disorders borrows from Kraupl-Taylor (1971) with its emphasis on actual or increased risk of significant distress, disability, or loss of freedom. Kraupl-Taylor stated that the disorder must be abnormal by the standards of the population or the norms of the individual and associated with concern experienced by the sufferer, other people, or doctors. The use of antidepressants to treat minor mood fluctuations and psychological problems in general has been condemned by Lader.(1998) Wing & Morris (1981) define *impairment* as loss of normal function at the organ level, e.g. renal or cerebral impairment, poor sight, or low IQ. *Disability* occurs at the level of the person as a result of impairments, poor exercise tolerance due to compromised pulmonary function. Handicap refers to disadvantages due to impairment and disability, as when one person suffers more because he hoped to continue sprint running, despite equal lung damage to a second person. In schizophrenia, for example, contributions to disability and handicap may arise from psychiatric impairment, such as social withdrawal and delusions, social disadvantages, like poor education level or lack of social support, and adverse personal reactions (low self-esteem, social discrimination) to impairments and disadvantages.

A statistically significant positive correlation between certain variables is not synonymous necessarily with a common causation⁵⁸¹. It could be due to such factors as shared high frequencies.

A physical 'lesion' is something like a malignant tumour, a bruise, a torn ligament, atrophic or dysplastic tissue, or a thrombus. Philosophers argue among themselves about what terminology most suits the constellation of problems psychiatrists deal with.(Dubos, 1968; Steiner, 1969; Davies, 1974; Mahler, 1975; Sedgwick, 1982) Is a disease something which we can isolate from the human body (e.g. bacteria) which is known to be associated with bodily reactions (e.g. tumour, pneumonia)? Is it a malfunction of some organ or tissue regardless of whether the aetiology is known or not? Did pernicious anaemia only become a disease with the discovery of cyanocobalmin or intrinsic factor? Is disease a term applicable to suffering regardless of knowledge of aetiology? Is the mind a distinct entity from the brain? Is the mind synonymous with the soul? Can all three, or two, become ill or diseased. René Descartes separated mind from body and thought from feeling, with profound implications for psychiatric thinking.

Psychiatrists are sometimes accused of being too expansionist, taking over the management of problems of living,(Double, 2002) or of being too restrictive in the territory which they define as their own.

The *medical model*⁵⁸² (Macklin, 1973; Berrios & Marková, 2002) assumes that one day we will discover a physical cause or mechanism for most, if not all, psychological ills, or, more narrowly, for certain psychological problems, such as psychotic states. Craddock et al (2008) are critical of attempts to downgrade medical aspects of care, viewing it as disadvantaging patients. Psychoanalysts interpret the psychoses as the loss of firm ego boundaries with intrusion of repressed noxious material into consciousness. The pure organic psychiatrist might view psychological/ behavioural problems as manifestations of brain dysfunction, however subtle the latter may be. It could be argued that at least some psychiatric problems are simply a way of communicating distress⁵⁸³, avoiding painful stresses, or evading

⁵⁸⁰ In practice, patients often have symptoms of more than one disorder or fulfil criteria for multiple disorders.(McGuffin, 2002, p. 11)

⁵⁸¹ H T Buckle (1821-62) wrote that 'in all fields of inquiry there are a sufficient number of empirical coincidences to make a plausible case in favour of whatever view a man chooses to advocate.(Buckle, 1857, p. 162) Raymond Pearl (1879-1940) of Johns Hopkins University infected cancer patients with tubercle bacilli because he concluded that the two diseases rarely occurred together and must therefore antagonise one another!(Pyenson & Sheets-Pyenson, 1999, p. 283)

⁵⁸² René Descartes (Renatus Cartesius), 1596-1650, Jesuit-trained father of modern philosophy, was born at La Haye near Tours. Descartes's separation of mind from body and thought from feeling had major implications for psychiatric thinking. Unlike Freud, he asserted that mental processes are limited to conscious awareness.

⁵⁸³ Jacob (2009), for example, is justly critical of the DSM concept of major depression. There are serious shortcomings attached to diagnosing depression by employing severity criteria and a cross-sectional examination. Major depression is a loosely defined category that trumps adjustment disorder and dysthymia. Jacob (2009) pleads for an emphasis on context (stress, coping, and support), a return to older categories (melancholia, dysthymia, and adjustment disorder), and avoidance of medicalisation of distress.

responsibilities, or, bluntly, of 'milking the system'. We do not know many of the answers to such questions and it is likely that all the various theories are true to some extent in some people some of the time. What brings a person to a psychiatrist or other mental health professional is rarely simple. Diseases, disorders, or whatever do not occur in a vacuum. They are dependent on many variables for their expression, e.g. genetics, upbringing, nutrition, peer group influences, cultural mores, drug intake, socio-economic status, education, and age.

The terms endogenous and exogenous were introduced into medicine by the neurologist Mobius in 1893. Their usefulness, like so many other terms, has not been straightforward, and modern practice assumes contributions from biological, psychological and environmental sources. Johnstone, ea,(1988) could not distinguish between organic and DSM-III -diagnosed, matched 'functional' (schizophrenia, mania, depression) cases on the PSE.

Aetiology is rarely known in psychiatry, except for problems like grief or diseases like syphilis.⁵⁸⁴ We are describing syndromes. There is no other practical alternative at present, unless we are to become enslaved by theory.

No matter what the diagnosis or however chronic the illness, we must not regard patients as objects.(Hinshelwood, 1999)

Diagnostic levels (Stanga & Preskorn, 1997)

Symptom detection - most basic form⁵⁸⁵

Syndromic diagnoses – majority of psychiatric practice⁵⁸⁶

Pathophysiological diagnosis - even better

Aetiological diagnosis - the ideal

One can view mental experience from the point of view of either *form* or *function*. The former model sees people as animals subject to various diseases that present in certain ways. This approach attempts to apply scientific objectivity to the understanding of a dysfunctional nervous system. The latter model grants pre-eminence to empathising with the mental/psychological activity of independent human agents. As pointed out by McHugh and Slavney,(1986) the approach from form asks 'what' (is the patient suffering from) whereas the approach from function asks 'why' (is he feeling, thinking, or behaving in this way)? Some disorders lend themselves to one approach more than another when different questions are being asked, e.g. dementia lends itself to form when we are considering aetiology but less so when we are talking about individual reactions to the news that one is suffering from dementia. However, life is not simple and there are many perspectives that allow us to conceptualise suffering or dysfunction, e.g. spiritual, behavioural/learning, medical/disease/disorder/categorical, dimensions, and the individual life narrative. The idea that medical diagnoses are less value-laden than psychiatric ones is untrue.(Fulford, 1989) Finally, *animal models (AMs) of human disorders* are many. Human beings live for longer than lower animals and their brains are not as readily accessible as other species. This has led to a search for analogies between humans and lesser creatures. Certain theories about human development, such as that of John Bowlby⁵⁸⁷, drew on earlier animal work.(Shapiro & Hertzog, 2003) The *olfactory bulbectomised rat* was discovered coincidentally to lead to a state reminiscent of depression during the 1970s. This model also shows immune and endocrine abnormalities similar to those reported in human depressives.(Kelly ea, 1997) Such changes are reversed by antidepressants, and the fact that the 5-HT₂ antagonist metergoline can

⁵⁸⁴ The Latin phrase *post hoc ergo propter hoc* refers to the error of logic wherein sequence is confused with aetiology.

⁵⁸⁵ However, Murray (2002) would suggest that many normals experience hallucinations and delusions, and suggests that schizophrenia may be at one end of a spectrum with 'normality' occupying the other extreme. Van Os (2002; Verdoux & van Os, 2002) points out that 13% of the Dutch population experience a 'psychotic' episode but only a distressed 4% seek help – he says that normal people experience psychotic symptoms and that it is the attributions they attach to such experiences, perhaps based on childhood neuroticism, that leads to distress and hence to psychosis; also, clinicians diagnosed psychosis in 0.7% of cases compared to 28.4% with screening instruments. Wiles ea,(2006) in an 18-month British follow-up study, found that 4.4% of the general population reported incident psychotic symptoms, risk factors for which included rural abode, poor social support, adverse life events, smoking tobacco, neurotic symptoms, and harmful drinking.

⁵⁸⁶ Having the same syndrome usually infers that the same symptoms are shared, but not necessarily the same aetiology.

⁵⁸⁷ E.g. **Bowlby** described 3 main *attachment patterns*: *secure* (confident explorers), *anxious-resistant* (afraid of separation and is clingy and unwilling to explore), and *anxious-avoidant* (lacks confidence that care will be given – extreme cases are found in badly run institutions).

reverse the effects of antidepressants suggests that bulbectomy involves mainly serotonergic mechanisms. Willner and Mitchell (2002) consider the *chronic mild stress model* to be most valid AM of depression available, although it is difficult to implement reliably. Animals that are subordinate or have lost their place in a *social hierarchy* constitute another AM for depression. The naïve/subordinate male tree shrew (*Tupaia belangeri*, diurnal SE Asia) develops a number of changes when exposed to an experienced/dominant male of the same species that are reminiscent of depression in humans (decreased motoric behaviour and intake of food, decreased weight of body and gonads, decreased plasma testosterone, increase in adrenal weight and urinary cortisol, reduced slow-wave sleep, broken sleep, early morning waking, down-regulation of glucocorticoid receptors, down-regulation of CRH receptors, down-regulation of 5-HT1A and alpha-2-adrenoceptors in certain brain regions, one-tenth decrease in volume of hippocampal formation, inhibition of dentate gyrus granule precursor cell proliferation, and pyramidal cell apical dendritic retraction in hippocampal CA3), although uniquely human attributes such as suicidal ideation are impossible to model in this paradigm. Clomipramine leads to a delayed recovery from these changes (Fuchs et al., 1996) whereas diazepam is ineffective in this AM. (Fuchs, 2004)

The *spontaneously hypertensive rat* has been used to model attention deficit hyperactivity disorder. Animals may be specially bred to mimic human conditions, e.g. Flinders Low Sensitive Line of rats (depression). *Transgenic mice* with an excess of CAG repeats in the Huntington's disease gene have been created: they demonstrate progressive motor and behaviour disturbance. (Reddy et al., 1998) AMs of schizophrenia, such as the *apomorphine-susceptible Wistar rat* (strong gnawing response to apomorphine) and the *heterozygous haploinsufficient reeler mouse* (expresses only half the brain reelin content [reelin⁵⁸⁸ is a serine protease of the extracellular matrix that is expressed in adult brain, especially cerebral cortex, and may be involved in synaptic plasticity] of wild⁵⁸⁹-type mice), are discussed by Ellenbroek and Cools (2002) and Lipska and Weinberger. (2003) The NMDA receptor may be hypofunctional in schizophrenia and transgenic mice with diminished expression of this receptor display behaviours reminiscent of schizophrenia. (Gainetdinov et al., 2001) Monkeys that have their dorsolateral prefrontal cortex lesioned in infancy may not demonstrate abnormal behaviour until they are mature, an observation that may be of assistance in understanding why a neurodevelopmental disorder such as schizophrenia does not usually become overt until at least the teenage years. (Weinberger, 1987) Escalating doses of amphetamine leads animals to develop attentional problems. Overexpression of D2 striatal receptors in transgenic mice may mimic some of the cognitive problems found in schizophrenia, e.g. working memory. (Kellendonk et al., 2006) During the acute phase attention is impaired and performance-associated ACh release is frozen; during remission (when attention is easily distracted) such animals produce excess cortical ACh in an attempt to boost performance; such deficits are modestly reduced by low doses of antipsychotic drugs; and the authors suggest that the deficits reflect impaired top-down control and abnormalities in fronto-mesolimbic-basal forebrain circuitry. (Sarter et al., 2008) Clozapine normalises dopaminergic turnover in monkey prefrontal cortex after dopamine turnover had been reduced with phencyclidine, which may explain, at least in part, the therapeutic actions of clozapine. (Elsworth et al., 2008) AMs of catatonia have been reviewed by Kaner (2004) and can be collectively referred to as *behavioural arrest* (induced immobility), e.g. spontaneous when generated by confrontation by a predator, manipulation-induced as when an animal is held immobile on its back, or drug-induced as with antipsychotic drugs⁵⁹⁰.

AMs of anxiety disorders are discussed by Graeff and Zangrossi. (2002) They divide these into those for generalised anxiety disorder (GAD: exposing a rat to a cat, time spent in the dark versus the light by mice, a startle response, and the tendency for rodents to bury an object that they are scared of), panic disorder

⁵⁸⁸ Protein derived from Reeler mouse mutant. Derived from Cajal-Retzius interneurons (may be GABA-ergic) that appear in layer I and interact during early development with the deeper Martinotti cells. Plays a role in formation of laminar patterns. It provides radially migrating cells with positional information. If reelin is absent (Reeler mouse or Kawasaki rat) the cortex forms in the wrong order, i.e. younger cells will settle in the wrong order by age (in normal corticogenesis neurons migrate outwards to form the pre-plate – the latter is populated by neurons where younger cells occupy positions beneath older cells). Homozygosity for the mutated reelin gene causes lissencephaly in humans: a 4-layered cortex with pyramidal cells occupying the incorrect layer. Reelin and GAD67 mRNA have been reported as decreased in (mainly) layer I in schizophrenia and bipolar disorder. (Impagnatiello et al., 1998)

⁵⁸⁹ Alleles can either (i) the normal or 'wild' type (found in the Wild) or (ii) the disease/mutant type.

⁵⁹⁰ High doses of antipsychotic drugs induce severe immobilisation (cataleptic state): a conscious animal crouches in a hunched position, will maintain an uncomfortable imposed posture for a number of minutes, and will move normally under extreme conditions (e.g. a cat is introduced into the mouse's cage) but such movement only lasts as long as the provocation lasts. Because such catalepsy is considered to be due to involvement of the basal ganglia (blockade of dopamine receptors) it is often employed as a model for drug-induced Parkinsonism.

(defensive behaviour of wild rats approached by a human, various forms of stimulation of the dorsal periaqueductal grey matter and dorso-medial hypothalamus), combined GAD and panic disorder (mouse flight following approach of rat, rat's fear of heights and openness [elevated T-maze]), specific phobias (e.g. cat odour test), and OCD (e.g. acral lick dermatitis). Quinpirole, a D2/D3 receptor agonist, causes rats to check excessively (Dvorkin ea, 2006), a putative model of OCD. Early blockade of serotonin transporters with fluoxetine in the mouse leads to anxious adult mice.(Ansorge ea, 2004) Memory consolidation depends on protein synthesis and preventing this might prevent PTSD. Rats given the protein synthesis inhibitor anisomycin (too toxic to give to humans) reduces conditioned fear responses.(Cohen ea, 2003)

AMs of eating disorders, such as the *'tubby mouse'* (a recessive mutation causing maturity-onset obesity, insulin resistance, and degeneration of retina and cochlea) are discussed by Johansen and Schalling.(2002) Among attempts to model aspects of personality disorder is the breeding of rats to be high or low responders to novelty, e.g. high responders show a greater increase in dopamine in the nucleus accumbens when stressed, a greater release of corticosteroids when stressed, and learn to self-administer stimulant drugs faster, than do low responders.(Cools & Ellenbroek, 2002) According to Mayfield ea (2003, p. 849), with few exceptions (e.g. LSD), drugs that animals will not learn to self-administer are not abused by humans. The LSD case has been explained by 'a peculiarly human urge to seek altered states of consciousness'. Nevertheless, the present author has been intrigued by the idiosyncratic nature of some cases of drug abuse, e.g. a young woman who took large amounts of ampicillin on a regular basis. The so-called *clock mouse* has a genetic mutation affecting circadian rhythmicity. If this mouse is deprived of light it develops a prolonged (28 hour) period. It is one AM for sleep disorders.(Viaterna ea, 1994) A mutation in the so-called 'CLOCK' gene causes the mouse to become overactive, sleep less, and appear 'manic'.(Roybal ea, 2007)

One feline AM of mild head injury is induced by fluid-percussion under brief anaesthesia. The cats have no macroscopic brain lesions but do have extensive damage to axons. Photic induction of seizures in Senegalese baboons is used as one AM of human epilepsy and induction of seizures in rodents by electroshock or drugs⁵⁹¹ is employed to screen for anticonvulsant pharmaceuticals. One AM of Huntington's disease involves the mitochondrial toxin 3NP with possible NMDA-induced excitotoxicity.(Perez-De la Cruz & Santamaria, 2007) APP/PS1 transgenic mice have increased plasma clusterin⁵⁹², age-dependent increase in brain clusterin, and co-localised clusterin and amyloid in plaques whereas, in humans, excess clusterin is associated with various pathological indices of Alzheimer disease.(Thambisetty ea, 2010) In mice, preprohypocretin gene knockout or ataxin-3 driven hypocretin cell loss have been used to model narcolepsy.(Mignot ea, 2002)

Research & epidemiology⁵⁹³

'...when a disorder of unknown cause appears to be increasing in civilised countries, the effects of luxury, idleness, debauchery and town life were blamed'.(Hare, 1998)

'In our current state of development in psychiatry it is essential that we eschew long-established tendencies to theorise rather than experiment and to explain rather than correlate'.(Munro, 1999)

'The reasons why some researchers believe that a continuous number can issue out of the arithmetic addition of qualitative decisions is one of the mysteries of psychiatric psychometry'.(Berrios & Marková, 2002)

'The influence of the pharmaceutical industry on academic medicine in pervasive....Academic psychiatry is not for sale'.(Healy & Thase, 2003)

(In answer to the question: Do you think that psychiatry and psychiatric research are any further forward?) 'Not much, if at all; and, in clinical settings, there has been a deterioration'.(Wilkinson, 2003)

'Creating pseudo-entities such as 'major depression' for use as the principal 'diagnostic' measure increases the chance of non-differential results between interventions'.(Parker ea, 2003)

A researcher should carefully decide on what it is that it is hoped to prove or disprove (hypotheses) before embarking on the research itself. Otherwise p-values are meaningless! If one uses one statistical test at $p < 0.5$ there is a 5% chance of finding at least one false-positive result (*experiment-wise error rate*). If 10 tests are employed then this probability jumps to 41%!

⁵⁹¹ Pentylentetrazol, picrotoxin, bicuculline.

⁵⁹² Clusterin is involved in amyloid formation and clearance.

⁵⁹³ After decades of research most common psychiatric illness remains idiopathic. We have acres of correlations but little of concrete use in individual cases. The great majority of published research comes from wealthy countries.(Saxena ea, 2006)

Critical analysis of published research⁵⁹⁴ is now an established component of the MRCPsych II examination. (Greenhalgh, 1997; Lewis et al, 1997; Hotopf, 2000; Grimes & Schulz, 2002) Most research on drug treatments is too short and many employ a patient group that would be difficult to find in clinical practice, e.g. young⁵⁹⁵ non-female adults lacking comorbidity. Relatively healthy recruits (Geddes & Cipriani, 2004) and multi-site studies (Bridges et al, 2009) may account for very high placebo response rates. Selective publishing of trials may exaggerate positive results. (Turner et al, 2008) Drug research is largely funded by industry with non-commercial funding of trials being increasingly difficult to get. The RCPsych (2008) provides guidance on relationships with sponsors. Grunze (2009; Grunze et al, 2009) drew attention to 'sponsor bias' in relation to comparative efficacy of antipsychotic drugs.⁵⁹⁶ Ghost authorship (major contributor remains unmentioned, often a sponsoring company's statistician) is a worry. (Hargreaves, 2007) Research in psychotherapy is covered in the various chapters on individual disorders and in the chapter devoted to psychotherapy. Psychosocial therapies may be of such a high standard in research that the average busy service could not hope to emulate them.

Some fallacies

Ecological fallacy - erroneous attribution of causality to an observed ecological finding, e.g. because schizophrenia is more common in socio-economically deprived areas, then schizophrenia is due to socio-economic disadvantage, totally ignoring other possible explanations for the association, e.g. infection, childhood nutrition, some aspect of urban life, or downward social drift due to (fully or partially penetrant) illness

Berkson's bias (or fallacy) - making of false associations as a result of biased sampling (Berkson, 1949): classic example is the false assumption that institutionalised schizophrenics were immune from epilepsy and would therefore benefit from iatrogenic seizures, the original thinking behind convulsive therapy; since people with multiple disorders are more likely to seek treatment it should not surprise us to find high comorbidity in clinical (versus population-based) samples. (Bennett & Gjonbalaj-Morovic, 2007, p. 35)

Pilot studies are studies that are meant to test the water for bigger studies (although they often do not). They usually involve relatively small numbers and may last for relatively brief time periods. They may be used in negotiations for procuring finance for larger studies. An example of a pilot study is that by González-Isasi et al (2010) wherein patients with refractory bipolar disorder (BP) were randomised to usual medication or medication plus 'psychosocial treatment based on cognitive-behavioural' principles (adjuvant intervention). The authors found that the adjuvant group demonstrated improved functioning but the difference between the two groups did not reach statistical significance until 12 months had passed. Would this difference be maintained in a larger study and what about clinical significance (a major question when one considers the time and effort involved)? Also, how simply and seamlessly can the adjuvant intervention be employed (i.e. is the complete package required)?

Ecological studies involve scrutiny of a population as a whole. Outcomes are correlated with aggregate risk factor exposure. Such studies have low generalisability because we know little about the individuals involved and we lack temporal data.

*Case-control studies*⁵⁹⁷ are more appropriate for rare disorders like schizophrenia or for conditions that have very long latent periods. A random sample of cases of the disease under study is compared with a random sample of people who do not have the disease. Such studies are by their nature retrospective and subject to recall bias.

⁵⁹⁴ E.g. If the authors exclude the third of elderly medical inpatients who haven't the capacity to agree to be included in their study they cannot expect to detect disorders that reduce capacity in the remainder. (Holmes, 2008, p. 345)

⁵⁹⁵ The European Parliament approved legislation in 2006 (1901/2006) that insists on high quality research on drugs used for children. (Choonara, 2007)

⁵⁹⁶ Depending on the study: drug A > drug B > drug C > drug A, etc!

⁵⁹⁷ Case-control studies employ an *odds ratio* (approximate of relative incidence rates) to see if exposure or non-exposure to an event determines outcome.

*Self-controlled case series*⁵⁹⁸ (*case series method*) can be employed to examine the association between an acute event (e.g. stroke) and a (retrospectively ascertained) transient exposure (e.g. antipsychotic drugs) using cases only, i.e. no control subjects are required. There is implicit control of fixed multiplicative non-varying (over study period) confounders that act proportionally on baseline risk. This method is almost as efficient as the cohort method when periods of risk are brief relative to total period of observation. (e.g. Douglas & Smeeth, 2008)

The *nested case-control study* looks at cases with recent onset of the disorder of interest in an ongoing cohort study and compares these with suitable controls from the same cohort study for exposures that would be too costly or extremely difficult to have measured at the commencement of the study.

Cross-sectional surveys (point prevalence studies) look at defined total populations (all inpatients, all persons of a specified age group, etc) simultaneously (prognosis, risk factors, etc) and may be used to define the extent of a disorder, to compare findings with those in other groups, to plan services, or (if the study is repeated) to look for trends. Differences in outcome rates between those exposed to an event versus those not so exposed can be measured. Positive do not necessarily imply causality. Point prevalence rates are influenced by the rate at which an outcome develops and by the duration (chronicity) of the disorder.⁵⁹⁹ This type of research is not appropriate for the study of relatively rare phenomena (including major mental disorders).

Cohort studies compare the incidence of new cases of the disorder being studied in people who either have been exposed or not exposed to a theoretical risk factor: a *cohort study* is a longitudinal study of selected groups of individuals who are free of a disorder at the start of the study, and who differ in the level of exposure to a possible cause of the disorder. The association between outcome and exposure is expressed as relative risk (RR) which is the ratio between the incidence rates in those with the risk factor and the incidence rates in those without the risk factor. A *case register* is a local system that records the contacts with designated medical and social services for a defined geographical area.

Controlled trials may be open (patient and physician aware of drug taken), single-blind (doctors knows but patient does not know), double-blind (neither the doctor nor the patient is in the know), or triple-blind (patient, physician, and person evaluating outcome do not know). We work in the era of the *randomised controlled trial (RCT)*⁶⁰⁰. An RCT is a cohort study where the researcher controls level of exposure and participants are randomly assigned to different exposures (e.g. a medication). 'Non-exposed' individuals might receive 'treatment as usual' or a placebo (as distinct from a *head-to head trial* where two supposed active treatments are the subject of randomisation). Randomisation increases the ability of researchers to invoke causation, e.g. drug X is an antidepressant because it was significantly superior to placebo on Y's depression scale. Blinding is not as easy as many researchers might hope, e.g. how does one conceal the fact that a patient is receiving psychoanalysis or not developing extrapyramidal side effects from a medication? Also, acceptable placebo conditions are not always easy to conjure up.

In a *crossover study* the intervention of interest (A) and the control intervention (B) are administered to two randomised groups, (a) and (b) respectively. Then, following a washout period⁶⁰¹, patients swap over so that B is given to a and A is given to b. This allows the researcher to measure the difference between A and B for each patient. This design is more useful for pharmacotherapy trials than for psychotherapeutic studies, the effects of drug treatments being more or less nullified by the washout.

Internal validity of a study infers that the researchers measured what they intended to measure. *External validity* means that one can generalise from a study's findings to the wider world of clinical practice.

Selection bias infers that groups being studied are not comparable. *Information bias* is the result of gathering information in a different way for the various groups that the researcher is trying to compare with one another.

⁵⁹⁸ Case series studies are an example of a *descriptive study*: description of health status of more than one person. No comparison subjects are included.

⁵⁹⁹ 6-month prevalence of bipolar affective disorder is not much lower than lifetime prevalence because the disorder lasts for life and is recurrent.

⁶⁰⁰ *Cluster RCTs* are employed where the unit of randomisation is an area or organisation (e.g. hospital or GP practice) rather than the patient. When a single patient is a member of a group (e.g. in a nursing home) an intervention will have knock-on effects on other residents. Large numbers are needed to show significant differences. (Ukoumunne et al, 1999)

⁶⁰¹ This means to wash out the effects of an intervention, e.g. to clear a drug from the body. How long this will require depends on the drug in question (half-life, lipid solubility, depot, etc).

Confounding variables⁶⁰² must be accounted for in research. When these cannot be controlled in the study design, they must be allowed for in the analysis. Overmatching is said to be present when inappropriate selection of control variables results in more being eliminated from a study than was intended by the researchers, including items that were hoped to be examined. Most controlled trials are too short in duration of follow up, too small in numbers of patients recruited, and poorly reported. (Thornley & Adams, 1998) *Efficacy* refers to the ability of an intervention to produce the observed or desired changes. *Effectiveness* asks whether the results can be generalised to clinical practice. *Efficiency* is the effectiveness of an intervention in relation to the resources it uses up⁶⁰³. *Effect size*⁶⁰⁴ in drug trials equals the mean response to a drug divided by its standard deviation,⁶⁰⁵ i.e. the clinical significance rather than the statistical significance. A large effect size favours a deduction of efficacy. (Harrison-Read & Tyrer, 1995) Statistical significance is not the same as clinical significance. (Meltzer & Fatemi, 1998) There is a world of clinical difference between a 'response' to a drug (e.g. a 50% drop in HAM-D scores) and the complete absence of symptoms. (Roose, 1997; Nierenberg et al., 2010) A remission is defined as a HAM-D score of 7 or less on HAM-D-17 or 3 or less on HAM-D-7 or 10 or less on MADRS.

In the *intention to treat* model in drug trials, all initially randomised patients are included in the analysis, no matter what happens to them thereafter. Ratings of dropouts are included in the final analysis and their last scores are usually carried through each assessment point. This approach may reduce active drug-placebo differences where poor toleration of side effects leads to early opting out from the study.

Official first admission rates are often markedly inflated because of ignorance on the part of compilers of prior admissions to institutions other than the one in question. (Kreitman, 1993) Healy (1991) warns us that 'simply achieving effects in clinical trials cannot be passed off as evidence of' imipramine equivalence. Rigid dose regimens used in trials are not feasible in clinical practice.

One of the problems with genetic research into alcoholism is the tendency to view it as a single entity, rather than breaking it down into its component parts (alcohol consumption, dependence, and related problems) and investigating each one separately. (Marshall & Murray, 1991)

The literature paints a picture of depression being extremely widespread, on the increase over the years, being inseparable from but worse than normal unhappiness, classically affecting women who are poor or people out of work, showing a very similar clinical pattern and incidence worldwide, and perhaps being a product of industrialisation. Definitions, readiness or ability to recollect or admit depression, age effects, cross-sectional, prospective, retrospective, and different population groups, are only some of the confounders involved. (Kendell, 1993)

In a *catch-up prospective study* cases are identified at the commencement of the follow-up period. Because cases who do well tend to drop out, cases followed up tend to be chronic. A *follow-back design* involves a retrospective study with case identification at follow-up. This is rarely used in practice and also tends to miss drop-outs.

Lasagna's law

The rate of subjects for research will fall by at least half just as a study commences.

Equivalence trials try to determine if various treatments give similar benefits. Results are usually expressed as a *hazard ratio* (HR: ratio of response to treatment being studied to that of the comparator, the latter being a known effective intervention) with its 95% confidence intervals (CI). A HR circa unity and CI of 0.9-1.1 = probably equivalent; HR of 0.5 and CI = 0.3-0.7 = probably not equivalent; and HR 2.0 and CI = 1.7-2.3 = novel treatment probably inferior to comparator.

Reviews may be *traditional (narrative)* - a qualitative overview from a respected expert) or *systematic* (e.g. clear definition of why studies are accepted following by a meta-analysis). There are many sources of

⁶⁰² Distortion of a measure by exposure of subjects to factors other than the index factor.

⁶⁰³ E.g. cost-effectiveness or cost-benefit.

⁶⁰⁴ Effect sizes are essential to the computation of statistical power. They are the basis of meta-analysis. Effect sizes of 0.2, 0.5, and 0.8 would normally be considered as small, moderate, and large respectively.

⁶⁰⁵ Effect size = $\frac{\text{effect of experimental group} - \text{effect of control group}}{\text{SD of their differences}}$

studies for reviews, e.g. manual searches, conferences, *EMBASE*, *MEDLINE*, *PsycLIT*, and the *Cochrane Controlled Trials Register*. The latter is one of the services supplied by the Cochrane Collaboration (<http://hiru.mcmaster.ca/cochrane/default.htm>), an international, not-for-profit organisation named after Archie Cochrane, a British epidemiologist.

Michael Shepherd (1988) defined epidemiology as 'the mass aspects of disease'. A more conventional definition would be 'the population-based quantitative study of the distribution, determinants and control of disease'. (Lewis & Mann, 1992) Stromgren preferred the word *endemiology* because so many of the conditions studied are endemic to the population, rather than epidemic.

An *at-risk population* is a group of people within a population who are at risk of developing a particular disorder. This must be taken into account in epidemiological studies, e.g. in underdeveloped countries the percentage of the population under a certain age may be higher than in the West, which may influence the overall percentage of the population with diagnosable schizophrenia. There are 3 common indices of risk. *Absolute risk* is the incidence rate of the disease among people exposed to an agent, assuming that non-exposure does not increase risk. It is best to compare the risk of disorder among exposed persons under investigation with those not so exposed. *Relative risk* is the ratio of the incidence rate in the exposed group to that in the non-exposed group. This is sometimes expressed as a percentage. It measures the proportionate increase (decrease if agent is protective) in disorder/disease rates of the exposed group. Lastly, *attributable risk* is the difference between the incidence rates in the exposed and non-exposed groups, in other words the risk attributable to the factor being investigated.⁶⁰⁶

Certain considerations are necessary before attributing cause. Exposure to the putative cause must always precede onset⁶⁰⁷ of the disorder (time sequence consideration). The spatial distribution of the disorder should be similar to that of the suspected cause. The incidence of disorder should correlate with the amount and duration of exposure to the suggested cause. The same association with a suspected causal agent (SCA) should be found in studies of different populations. However, failure to find such consistency may be due to differences in study design. Also, this may be a tall order in a discipline characterised by multifactorial aetiologies. Biological plausibility means that the association between disorder and exposure to SCA should be consistent with the known biological activity of the SCA. The disease or disorder should be reproducible in experimental animal models. Control or removal of the SCA should reduce the incidence of the condition under study.

According to Marshall ea.(2000) people who devise new scales for their study are more likely to report statistically significant results than are those using scales that are already standardised and known.

A *risk factor* is not necessarily synonymous with a cause: it may be a marker of another causal process or a causal factor itself. Disorders, such as suicide, schizophrenia or arterial hypertension, are often associated with numerous risk factors. Multiple measures of outcome increase the likelihood of unearthing a statistically significant difference purely as a result of chance.

A *mediator* is a variable that accounts completely or in part for the statistical relation found between a risk factor and a disorder. A *moderator* reduces or enhances the effects of a risk factor, e.g. a warm relationship between parent and child may reduce the likelihood of someone subjected to early harsh discipline developing a conduct disorder (Rutter & Sroufe, 2000); in this case the relationship is a protective moderator or *buffer*.

Health services research is underdeveloped in Ireland.(Expert Group on Mental Health Policy, 2006, p. 210) The WHO (2001) suggests) four types of research that are needed in order to improve mental health delivery: **epidemiological data** is needed to prioritise and to design/evaluate interventions; research into **effectiveness** of interventions (as distinct from efficacy); policy/services research (training needs of professionals and understanding of impact of policy decisions; and **cost** of services.

Prevention in the community

The goals of prevention are to reduce the incidence (onset), prevalence (duration) and residual disability associated with a disorder.

⁶⁰⁶ Put another way, population attributable risk = prportion of a disorder that can be associated with exposure to a risk factor.(Caughlin ea, 1994)

⁶⁰⁷ It has been noted for many years that dating the onset of illness is at least difficult and sometimes 'dubious'.(Sanborn, 1894)

Prevention

Primary – preventing a disorder starting in the first place, e.g. teaching parenting skills, education about alcohol and substance misuse, enriching the environment of deprived children, crisis intervention following major life events, avoiding alcohol or giving folate periconceptually (this may not be working and fortification of food may be necessary: Ward ea, 2004; Walsh ea, 2007), diet for PKU, lead-free petrol, laws against child abuse, genetic counselling, and STD prevention

Secondary - reducing the duration of a disorder by early diagnosis and treatment, e.g. crisis intervention, public education, and child guidance clinics

Tertiary - decreasing the prevalence of residual defects and disabilities, enabling the person to reach the highest feasible level of function; psychiatric rehabilitation addresses the medical, psychiatric, and social needs of chronic patients; social needs include literacy, housing, employment, finance, and social and living skills

In summary: reduce incidence (primary), prevalence (secondary), and residual disability (tertiary).

The prevalence of mental illness is so high that the mental health workforce cannot help everyone. The focus tends to be on the more severe and chronic disorders. (Jorm, 2000) In some cases, this has meant a 'psychosis only' service. To date, efforts to improve public understanding lag behind those for other common illnesses. A void exists between beliefs about aetiology and management between doctors and the public at large that are greater than between 'primitive' healer and pre-scientific man. Most people believe that antidepressants are addictive and want counselling instead.⁶⁰⁸ Evidence for efficacy of counselling for depression is lacking. (Thompson, 1999; Baldwin, 2000)

Medical statistics⁶⁰⁹

'If you torture statistics, they'll confess to anything'. (Saying)

'Politicians, policymakers, and public-health professionals make complex decisions on the basis of estimates of disease burden from different sources, many of which are "marketed" by skilled advocates'. (Walker ea, 2007)

'We tend to search for or believe only those associations that fit in with our expectations'. (Simon, 2008)

The French physician Pierre Charles Alexandre Louis (1787-1872) was the first medical man to collect and numerically analyse data on patients⁶¹⁰. Statistics may refer to systematically collected numerical facts (e.g. vital or population statistics) or the science of collecting, classifying, and using data, particularly when these come in large quantities or numbers. (Hayslett, 1974; Pocock, 1980; Bourke ea, 1988; Altman, 1991; MacRae, 1992; McGuire, 1993) Statistical difference is not synonymous with clinical difference.

Investigators should seek advice on statistics at the study design stage and not when an amorphous mass of data has been collected! (Armitage ea, 2002)

Parametric statistics are those inferential statistics (assess meaning of data, e.g. the correlation coefficient or *Student's t test*⁶¹¹) that assume a normal distribution for data. The *power*⁶¹² of a study, in statistical jargon, refers to the probability that a type 2 error (Q.V.) will not be made, if indeed there is a real difference between 2 treatments. Power increases with the size of the study. *Non-parametric* statistics (e.g. χ^2 test), on the other hand, use material of non-normal distribution. Put another way, the methods of calculation power for categorical data (e.g. 'yes' or 'no' categories) are the non-parametric tests, whereas those for continuous data (e.g. graded tests for depression) are the parametric tests.

Prevalence means the total number of cases in a particular population at a given point in time (point prevalence) or over a period of time (period prevalence). A sample of prevalent cases will give an over-representation of chronic, poor prognosis cases. Factors associated with prevalent cases may lead to a poor

⁶⁰⁸ The author has noted (in 2010) that an Irish textbook designed for Junior Cert students warns about the 'addictive' nature of antidepressants!

⁶⁰⁹ See, e.g. Gonick and Smith (1993) for an introduction. *Statistics* derives from the German *Staat*, a State, because the State required information in order to guide policy.

⁶¹⁰ Louis distinguished typhus from typhoid and gave typhoid its name. He should not be confused with the French surgeon Antoine Louis (1723-1792) of Angle of Louis fame. The latter worked with Joseph Ignace Guillotin (1738-1814) on the guillotine.

⁶¹¹ The **t test (t-test)** is the optimal test to discover if the difference between means of 2 samples of subjects is likely the result of chance only. The **t test for dependent means** is the optimal test of significance for difference between means from 2 matched groups or treatment levels.

⁶¹² **Power** = probability of finding a true difference or relation between multiple measures with a given sample size.

prognosis without necessarily having a causative role. Retrospective and prospective studies may give wildly different prevalences⁶¹³ for common mental disorders for various reasons such as documentation issues and recall bias.

In order to seek causes one must study incident cases. *Incidence* refers to the number of new cases arising in a given period of time. A more precise measurement than incidence is the *inception rate* or the proportion of individuals in a population who are initially free of a disorder but who acquire it within a given interval of time. The term ‘incidence’ is often used loosely to mean the inception rate. *Cumulative incidence*⁶¹⁴ is the number of new cases divided by the total at-risk population over a specified period of time, say one year; this measure is useful in population numbers remain steady over the period in question. Epidemiologists often use *person-time* as the denominator⁶¹⁵, i.e. sum of time periods (such as person-years) of the observation for everyone in the population at risk: incidence rate = no. of new cases/person-years.

Statistical terms

*Analysis of covariance*⁶¹⁶ (ANCOVA): method used to determine if 2 or more related dependent variables that are exposed to 2 or more related variables differ significantly (more than chance), e.g. a researcher who is comparing a drug and exercise in order to determine their effects on the weight of obese patients will include pre-study weight⁶¹⁷ as a *covariate* (a covariate is a variable that the researcher believes may influence outcome [*dependent variable/endpoint*] and that needs to be adjusted for statistically).

Analysis of variance (ANOVA): test comparing mean values from at least 2 groups. Multivariate analysis of variance (MANOVA), a generalised form of ANOVA, may be used when multiple dependent variables are assessed at the same time.

Bias: a distorting influence that renders study results an inaccurate reflection of reality, e.g. ‘selection bias’ occurs when only acute patients enter one arm of a comparative study of two antidepressant drugs and chronic patients occupy the other arm.

Bivariate correlational analysis: provides a single number summarising the relationship between 2 variables.

Chi² test: assesses if a significant difference exists between an observed number of responses in any category and an expected number based on the null hypothesis.

Cluster analysis: a data reduction technique used to group subjects into subgroups based on how they are alike or different on a set of variables; it can produce clusters/categories (based on similarities or differences) but not dimensions. The idea of using clusters as a basis of classifying psychiatric disorders has been dismissed by Jablensky (2009) because of the likely necessity of increasing complexity in clinical thinking as we strive to incorporate new data into the way we work.

Clustering of disorders: statistically, the average GP should have 4 cases of the autosomal dominant disorder heterozygous familial hypercholesterolaemia (1 in 500 people) but the actual figure varies because of clustering within families; the geographical prevalence of Huntington’s disease (autosomal dominant; 1 in 20,000) also varies for the same reason.

Confidence interval: measure of range of values within which true population value is believed to lie.

Confounding factor: something that explains a particular outcome in a study but has an independent relationship to another factor that does not exert a causal influence.

⁶¹³ A study (Moffitt et al., 2010) comparing a prospective New Zealand birth cohort that involved a 32-year follow-up with 96% retention (the percentage of original cases that could be studied throughout the duration of the study) gave prevalences for anxiety, depression, alcohol dependence, and cannabis dependence that were about double those reported in 2 US (retrospective) national comorbidity studies (NCS and NCS-R)!

⁶¹⁴ The specified time is written t_0 to t_1 . **Cumulative incidence** (CI) = Number of new cases, t_0 to t_1 /population at risk at T_0 , where the denominator = total number of persons at risk for the event at T_0 (the start of the time period). Do not include people at T_0 who have the disorder or experienced the event in question in the denominator. **Incidence density** (ID) is a superior measure of rate of occurrence of new events in unstable populations (where numbers change for any reason, such as assumption of ‘caseness’, demise, or uncontactability). ID = Number of new cases, t_0 to t_1 /total person-time of observation. The denominator includes the population at risk for the event in question and has to be adjusted due to drop-outs (e.g. death or loss to follow-up).

⁶¹⁵ For those who have forgotten the denominator is below the line, e.g. in $\frac{1}{2}$ the numerator = 1 and the denominator = 2.

⁶¹⁶ The Kruskal-Wallis test, which compares medians in at least 2 groups, is a non-parametric version of ANOVA.

⁶¹⁷ Or, e.g., when comparing the effects of two antidepressant drugs, baseline depression scores are a covariate.

Correlation coefficient (cc): measures relationship between 2 sets of variables without making any assumption about their dependence or independence: a cc of 1.0 means exact similarity, one of 0.0 infers no relationship.

Descriptive statistics: these simply summarise data, e.g. the mean that measures central tendency.

*Diagnostic test accuracy*⁶¹⁸: overall proportion of correct results when a test is applied to a sample or population.

Discriminant function analysis: used to statistically distinguish between at least 2 groups on the basis of discriminating variables.

Factor analysis: seeks smallest number of dimensions/variables that define a group; factors express the relationship between attributes, not between individuals; data reduction method used to reduce many variables to a smaller number of linear combinations of variables; sometimes attacked for showing anything that is sought by researchers! *Principal components analysis* resembles factor analysis and, like the latter, it requires continuous data; used where there is a need to reduce number of variables in an analysis but to explain the same amount of variance (factor analysis is employed where underlying unobserved factors/latent constructs are the focus of interest).

Funnel plot: bias in publication usually involves non-publication of small or negative studies; a funnel plot is used to plot study effect size against precision and can show up a void that small negative studies should occupy, i.e. funnel plot asymmetry.

Interquartile range (IQR): this provides an idea of the spread of values; numerical difference between values that are found a quarter way up from bottom of distribution and a quarter way down from top of distribution; used when values are not distributed evenly and when median value is known; the 2 values that define IQR encompass middle 50% of all the values in the distribution.

Kurtosis: a measure of peakedness or flatness of a curve.

Last observation carried forward was a traditional method of dealing with loss of patients to follow-up (missing data) in research. It has been replaced by so-called *principled methods*, e.g. multiple imputation.

Mann-Whitney U-test (Wilcoxon rank sum test): used to compare 2 groups of unmatched data (2 independent groups that are not normally distributed); the nonparametric equivalent of the t-test; it tests equality of medians only where distributions are of the same shape.

Mean: sum of scores divided by number of scores; it should be noted that the mean, mode, and median are synonymous in a normal distribution.

Median: the middle score, below, which half of the scores fall. The median is identified by ordering numbers according to size and then picking the middle one. If two values are the same (e.g. 100 and 102), then the median is the mean of these two values (i.e. 101 in this case).

Meta-analysis: statistical analysis of a large collection of analysis results from individual studies in order to integrate findings (to produce *summary statistic/s* – effect sizes from different studies are combined into a single estimate with associated confidence interval). When applied to controlled drug trials, the trials should be complete (i.e. include subjects with positive and negative results). The results of each trial are calculated in the form of an *odds ratio* based on comparing the number of patients in the experimental group reaching a defined end-point with the corresponding number in the control group. The odds ratio from each trial are then summarised using an appropriate test of statistical significance, and an estimate of the magnitude of the treatment effect⁶¹⁹ is made. This method overcomes the fact that the number of patients in individual trials is often small. One problem is that one does not always know how representative the patients are of those seen in clinical practice. Also, two meta-analyses of the same treatment do not necessarily reach the same conclusion! (Furukawa, 2004) *Cumulative meta-analysis* refers to the incorporation of new trials into the analysis. *Heterogeneity*, variations occurring between studies, may stem from statistics, methodology, or clinical variables, and may be sufficiently large make nonsense of meta-analysis. *Weighting* refers to the influence or weight that different studies may have on the results of meta-analysis, e.g. smaller numbers of participants in a study are given less weight than bigger numbers. When different studies employ different measures to assess the same outcome the statistician can combine the results using *standardised mean difference*⁶²⁰. The *forest plot* is a way of graphically summarising

⁶¹⁸ Patients with the disease and test positive + patients without the disease who test negative and divide total by the total sample and express result as a percentage.

⁶¹⁹ *Effect size* refers to group differences in standard deviation units on the normal distribution.

⁶²⁰ SMD = difference between mean results of treatment groups/pooled standard deviation.

results of a meta-analysis: the vertical line indicates equality between intervention of interest and control intervention and short horizontal lines show confidence intervals of outcomes of different studies with a square on such lines showing the weight of that study, and a diamond gives the overall summary statistic. A *mega-analysis* means that the raw data from different studies are employed as if they all belonged to one original study.

Minimisation: this is a way of allocating people to treatment groups in a study that does not use random allocation but, instead, uses means to deliberately reduce any imbalance between the groups that may be due to confounders, e.g. where one group has too many males you might add the next male to the other group.

Mode: most frequent score or most common value.

Multivariate analysis: method of examining the relation between 3 or more variables; techniques include multiple regression, discriminant analysis, canonical correlation, and factor analysis.

Multiple linear regression: used to predict a single continuous outcome variable from a set of continuous or dichotomous predictor variables.

Negative likelihood ratio: a measure of how much less likely than not a patient is to have the disorder in question if the test result is negative, i.e. $(1 - \text{sensitivity}) / \text{specificity}$.

Negative predictive value: the probability that a person has not got the disorder if the test result is negative.

Normal distribution: pattern for distribution for data set which follows a bell-shape curve; x-axis represents variables of interest (e.g. IQ or height) and y-axis represents number of people having a certain value of the variable; the curve decreases symmetrically either side of a peak, the latter representing the mean/middle variable.

Null hypothesis: the assumption that no difference exists (until one is shown to exist), i.e. that the difference between 2 groups is the result of chance or sampling error; a statistical strategy whereby it is assumed that there is no real difference between 2 variables, such as 2 treatments. The p-value is the probability that difference or association between variables is a result of chance (false positive). The threshold for statistical significance is arbitrarily set at 0.05 (meaning 5/100). If p equals or is less than this figure the null hypothesis (that there is no difference or association) is rejected. A p value of $P < 0.001$, by way of example, means that the odds of this difference between two rates happening by chance are less than one in a thousand, a highly significant statistical finding.

Number needed to treat (NNT): the number of cases that would have to be treated in a certain way in order to avoid one outcome event⁶²¹ $= 1 / \text{absolute risk reduction (AAR)}$, where AAR = control event rate minus experimental event rate (for an undesired outcome) expressed as a percentage. An NNT of > 10 usually denotes a good effect of the intervention/treatment.

Partial correlation analysis: a single number is provided to describe the relationship between certain variables, adjusting for the effect of other variables.

Population: entire collection of a set having the same definition.

Positive likelihood ratio: measure of how much more likely than not a patient is to have the disease if the test result is positive, i.e. $\text{sensitivity} / (1 - \text{specificity})$.

Positive predictive value: the proportion of true cases divided by the number scoring positive on the test, i.e. the probability that a person has the disorder if the test result is positive.

Range: measure of dispersion from lowest to highest score.

Rate: A figure determined by numerator (number of cases) divided by denominator (population at risk).

Reference range: this usually means the mean ± 1.96 standard deviations, where one expects to find the great majority of cases; it does not necessarily imply that values above or below the range are abnormal because they may simply be part of a continuum; extremely deviant findings (*outliers*), on the other hand, are likely to be discontinuous; interpretation of results often requires experience (age of patient, pregnancy, laboratory error, effects of disease or prescribed medications, factitious, comparison with previous findings, etc).

Regression: techniques used to develop complex models in order to examine role of one or several predictor variables on an outcome variable. *Logistic regression*: optimal technique to predict a binary outcome from a set of continuous or binary variables; gives probability value and odds ratio; used in research when outcome is either one thing or another, e.g. did the patient develop the illness or not?

⁶²¹ Or to obtain one success that would not be obtained with the control treatment. The number needed to harm (NNH) is another measure that would be useful to know.

Regression coefficient: measures relationship between 2 sets of variables, assuming one is dependent, the other independent; may be descriptive (summary of data) or inferential (assesses meaning of data).

Sample: subset of observations selected from a population.

Sample enrichment: method of narrowing down a sample so that it contains more of the variable being sought, e.g. picking a high-risk group for schizophrenia in order to study the pre-psychotic phase of that illness.

Skewness: measures deviation from normal distribution curve; non-symmetrical with one tail longer than the other at either side of the mean value.

Standard deviation (S.D.): square root of variance – 64% of scores in the normal distribution fall within one S.D. on either side of the mean.

Standard error: an estimate of discrepancy between the sample mean and the true population mean, or S.D. divided by square root of number of cases; this will shrink with an increase in sample size because bigger samples approach the characteristics of the population from which they are drawn.

Standard mortality ratio (SMR): observed number of deaths/expected number of deaths; the expected number is found by applying death rates of an external reference population to the age distribution of the study population. E.g., an SMR of, say, 5 means that the index group has a standard mortality rate five times that of the general population.

Standard (Z) score: the value-mean divided by the S.D.; specifies the position of a particular observation on the normal distribution.

Type 1 error: occurs when statistically significant result occurs by chance; a false positive; to regard a difference as significant when in fact it is not.⁶²²

Type 2 error: occurs when a real result is obscured by chance or random error; a false negative; a study fails to demonstrate a statistically significant effect that does in reality exist.

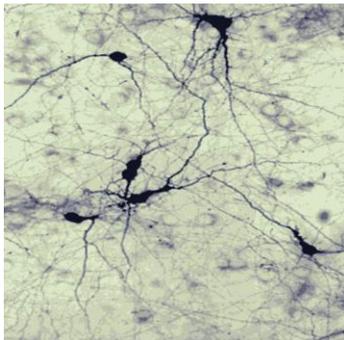
Variance: the squared S.D.

Wilcoxon signed-ranks test: used to compare 2 samples of matched data.

Neuroanatomy and neurophysiology

'As information is added to a computer, it gets slower, the exact opposite occurs with the brain'. (Trimble, 1996)

Nerve cells (neurones) and the interstitial cells (= neuroglia⁶²³ = oligodendrocytes and astrocytes) of the nervous system derive from ectoderm. Microglia (mesoglia) are of mesodermal origin. Glial cells, which possess almost the same receptors as are found on nerve cells, are likely to have neuromodulation and neurotransmission actions. They are not there simply to provide neuronal support. Nerve cells are born in proliferative zones around the ventricular lumen at a distance from their final locations. They must then migrate.



Neurones

CNS stem cells

Multipotent cells that can reproduce themselves or differentiate (so far) include:

⁶²² The usual approach used to balance the possibility of making type 1 or 2 errors is to set the value for P at less than or equal to 0.05.

⁶²³ Glia = glue (supportive and structural function). In multiple sclerosis there is an immune attack on myelin basic protein, the main protein in myelin, leading to failure of conduction of the action potential.

1. *Subventricular zone of lateral wall of lateral cerebral ventricle* – migrate to olfactory bulb and form interneurons – important for sense of smell
2. *Subgranular zone of dentate gyrus in hippocampal formation* – learning and memory functions

Glial cell types

Astrocytes (astroglia) – support (structure, nutrition, environment/ion concentration, maintenance of synaptic milieu, release of co-agonists needed for glutamate receptor function and transport of glutamate to end its action at synapse) the neurones and respond to nerve cell injury [fibroblast-like function leading to gliosis]; end-feet involved in blood-brain barrier; promote myelination by oligodendrocytes; may act as neural progenitor cells (Noctor et al., 2002); long-distance signalling between cells

Oligodendrocytes (oligodendroglia) – get their name from having few processes; myelin sheath formation
Microglia – immune function; rod-shaped when activated

Radial glial cells (RGCs) guide neurones during their migration and act as nerve cell progenitor cells in a number of brain areas. When the process of neurogenesis has finished, RGCs move from the zones of proliferation into the cortical mantle where they change into mature astrocytes. Astrocytes, the most common cell in the CNS, connect with nerve cells and blood vessels. The latter ‘perivascular foot’ forms the gliovascular membrane, one part of the blood-brain barrier. The capillary wall forms the other part of the blood-brain barrier. CNS capillary cells contain a transaminase that prevents GABA from entering the CNS by metabolising it. Nutrients and metabolites are exchanged between neurones and capillaries via a thick astrocytic process. Astrocytes enlarge following neuronal injury and move to the site of injury where they form a protective scar.

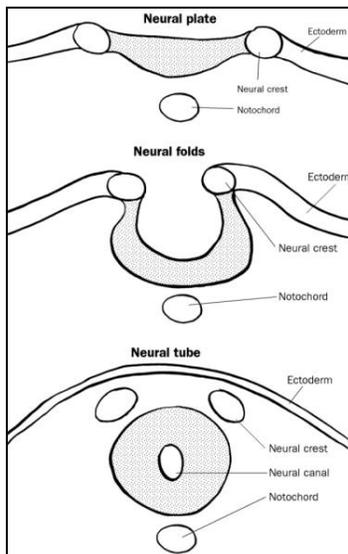
Oligodendrocytes⁶²⁴ in the CNS form myelin⁶²⁵. The manner in which each wrap themselves around axons differs, oligodendrocytes sending out processes to do so while Schwann cell bodies elongate themselves around axons. Specialised points along axons where the myelin sheath is thinned are called *nodes of Ranvier*. *Saltatory conduction* means that the nerve impulse jumps from one node of Ranvier to the next one, thus speeding up impulse propagation. The current travels in the intracellular fluid between the nodes and across the membrane at the nodes. Unmyelinated axons conduct (*continuous conduction*) more slowly and use more energy because they must utilise more Na⁺/K⁺ pumps in order to restore the resting membrane potential. Apart from myelin or the lack of it, the other factor determining speed of propagation of an action potential is axonal diameter: small and unmyelinated axons might conduct at half a metre per second whereas large and myelinated axons might conduct at 200 times that speed!

Microglia⁶²⁶ and cellular elements of cerebral blood vessels are the connective tissue of the nervous system. Microglia (thin, elongated cells with several thin processes) are phagocytic (scavenger) cells (‘macrophages of the brain’) that can travel long distances. They are the immune cells of the CNS. They remain dormant unless activated by insult to the brain.

⁶²⁴ Schwann cells (lemmocytes, neurilemma cells) in the peripheral nervous system.

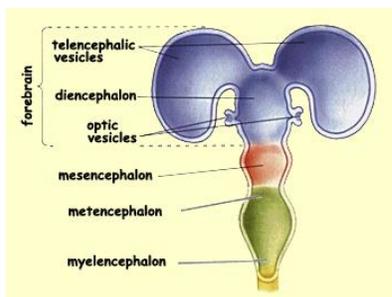
⁶²⁵ 70% lipids [cholesterol and phospholipids] and 30% proteins. Central (e.g. MS) and peripheral (as in some polyneuropathies) inflammatory demyelinating disorders are different processes and are rarely combined in the same patient.

⁶²⁶ Astrocytes and oligodendrocytes are known as macroglia.



Neural tube development

The early nervous system is a (neural) tube in the midline of the embryonic dorsal surface. The tube's cavity gives rise to the cerebral ventricles and the central canal of the spinal cord. Later on, there are 3 cerebral swellings (vesicles) at the oral end of the tube (head end of embryo): forebrain or prosencephalon, midbrain or mesencephalon, and hindbrain or rhombencephalon, the latter continuing into the spinal cord. The midbrain (includes the colliculi, red nucleus, substantia nigra, and periaqueductal gray) will change very little thereafter. Two secondary swellings, collectively the telencephalon, grow out from the forebrain, precursors of the cerebral hemispheres. The latter include the olfactory bulbs and lobes (rhinencephalon or 'smell brain'), the pallium (cerebral cortex), and the basal ganglia or corpus striatum. It should be recalled that the olfactory pathway represents the only sensory modality having direct access to the cerebral cortex without passing through the thalamus ('marriage bed'). Part of the forebrain, the diencephalon, remains undivided in the midline and comprises the thalamus, hypothalamus, epithalamus, subthalamus, and optic vesicle.



Cerebral vesicles

The hindbrain divides into two secondary swellings, the metencephalon (pons, oral part of medulla oblongata, and cerebellum) and the myelencephalon (caudal medulla). Therefore, from rostral to caudal one can now see telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon (see diagram).

The dividing CNS during early gestation (rostral to caudal)

Primary (4th week)

Secondary (5th week)

PROSENCEPHALON → TELEENCEPHALON + DIENCEPHALON

MESENCEPHALON → MESENCEPHALON

RHOMBENCEPHALON → METENCEPHALON + MYELENCEPHALON

The risk for neural tube defects is decreased by giving the mother folic acid supplements and by fortifying cereals. (Reece, 1991; Czeizel, 1993; McDonnell ea, 1999; De Wals ea, 2007) Similar prophylaxis may apply to orofacial clefts, although multiple vitamins may be required. (Shaw ea, 1995)

The cerebral cortex⁶²⁷ consists of a paleocortex or primary olfactory cortex, an archicortex or limbic formation, and a neocortex. The archicortex and the paleocortex have an allocortical structure, i.e. they are tri-layered and lack layers I-III.⁶²⁸ The neocortex (90% of the human cerebral cortex) is six-layered (isocortical).⁶²⁹ The limbic lobe consists of the hippocampal formation, mamillary nuclei⁶³⁰ and anterior thalamus, cingulate cortex and parahippocampal gyrus; confusingly, the 'limbic ('border') system' is often extended to include other structures such as the amygdala ('almond').⁶³¹ Functions of the limbic system are to heed somatic (interoceptive) sensations and to look for environmental threats (Jones ea, 2009), to integrate all this data, and then to determine threat magnitude and need for action, i.e. the system has a safety role.

The cerebellum is made up of the archicerebellum or nodulofloccular lobe, the paleocerebellum or anterior lobe, and the neocerebellum or posterior lobe, named in order of their phylogenetic appearance. The cerebellum (and indeed the basal ganglia, e.g. caudate atrophy in Huntington's disease) has a role in cognition, monitoring the temporal context of mentation.⁶³² It may also have a role in modulating emotion. (Leroi ea, 2002)

We can now look at some of these events from the point of view of their timing. After the third week in utero, the brain starts to form from the anterior neural tube. By 4 weeks, the forebrain, midbrain and hindbrain vesicles have formed. By the seventh week bulges will have appeared which go on developing to form the 2 cerebral hemispheres. The start of cerebellar growth is in the second month. In the latter half of pregnancy we see convolution of the cerebral hemispheres, dendritic growth, synapse⁶³³ formation, and axonal myelination. The volume of the newborn's brain is about one-tenth of what it will be at 20 years of age; it will reach 90% of its eventual volume at age 7 years. Brain weight doubles during the first year of life, and triples in 5 years, then being 90% of adult size. A mature man's brain weighs about 1,340 grams. Cortical neurones are formed in an inside-out fashion during neocortical development: the deepest layers are formed first and the neurones that form progressively outer layers must pass through earlier layers as they push into the cortical mantle, each wave travelling a longer distance than those preceding it. Essential to migration is intercellular signalling via cell-cell adhesion molecules (cross-talk between RGCs and travelling nerve cells). Other regulatory influences arise from neurotransmitters (via NMDA receptors) and reelin (see above).

The neuronal complement of the CNS⁶³⁴ is formed before birth but white matter, occupying one-half of the adult cerebral volume and consisting of axons invested with myelin, only begins to form during the middle trimester. By two years of age the process of forming white matter is nine-tenths complete, the remainder requiring many years and myelination may in fact extend to the end of the sixth decade. Myelination begins

⁶²⁷ The various parts of the cerebral cortex do not function as independent kingdoms. Instead they work in series with other cortical and subcortical areas and with larger circuitry. Cortical circuits have excitatory and inhibitory functions.

⁶²⁸ Numbered from brain's surface.

⁶²⁹ Liddle (2001, p. 44) has this classification wrong.

⁶³⁰ The mamillary bodies are classically affected in Korsakoff's syndrome.

⁶³¹ Murray (2004, p. 28) uses the term 'limbic music' to denote 'the existential, clinical, "raw feel" emanating from the patient, i.e. emotional body language. The 'paralimbic' regions include orbitofrontal cortex, temporal pole, insula, cingulate cortex, and parahippocampal cortex, wherein cognitive, emotional, and visceral inputs merge.

⁶³² Andreasen (2003) describes the **cerebellum** as a 'metron', monitoring/coordinating the sequencing of mental activities within the context of time. Lesions of the cerebellum (especially posterior cerebellum/vermis) lead to various cognitive and emotional problems that involve executive function, visuospatial discernment, personality, and language.

⁶³³ Term **synapse** (Gk. *syn*, with and *aptein*, to join – to join with [to clasp]) coined by London neurophysiologist Charles Scott Sherrington (1857-1952) in 1897. Golgi incorrectly opined that neurones were connected by a net or syncytium, whereas Ramon y Cajal correctly understood that they were separated by spaces (synapses). In fact, there are 2 types of synapse. In one type the pre- and post-synaptic cytoplasm is continuous (bridged junctions, e.g. in cardiac muscle) via connexions (resembling tubules) and allowing electrical transmission. In the other type (the chief CNS type) there is separation by a synaptic cleft (20-50 nm) and transmission is chemical.

⁶³⁴ Pyramidal cells migrate *radially* and form columns where each column contains cells from the same clone but interneurones derived from one cell (in the predecessor of the striatum, the ganglionic eminence) spread around the cortex by migrating *horizontally*. Apoptosis (programmed cell death) is important at all stages of brain formation.

caudally with the brain stem and cerebellum and proceeds in a rostral direction to include the diencephalon and cerebral hemispheres. (Filley, 2003)

Neurones grow in such a way that allows their dendrites to achieve very selective synaptic connections with neighbouring cells (*neural specificity*). Such specificity allows discrete and reliable information transfer between cells. *Neural plasticity* on the other hand is the ability to adapt synaptic connections according to use and disuse, a capability essential for memory and learning functions. This 'Hebbian' plasticity⁶³⁵ is based on the idea that several neurones receiving simultaneous stimulation will thereafter share extra synaptic connections; such increased connectivity is due to *long-term potentiation (LTP)*⁶³⁶ which is important in learning. The *critical period* concept states that some brain developmental tasks must occur during set periods of time; otherwise related abilities will be lost or diminished⁶³⁷. Apart from critical periods, the other major factor in LTP is *activity-dependent learning*: exposure to psychological and physical environmental stimulation leads to changes in the brain such as the way cells align themselves, increased spiny processes on dendrites, synaptogenesis, and variations in neurotransmitter concentrations. Neural plasticity therefore allows us to change in response to experiences during life and not to be a prisoner of our genetic inheritance or to become robotic clones of our parents.

The neuronal body⁶³⁸ contains neuroplasm and, in females, a paranuclear body, a nuclear satellite corresponding to the paired X-chromosomes. Neuroplasm also contains chromophilic Nissl substance, consisting of flattened membranous sacs to which ribosomes (RNA-containing granules) are attached. Nissl substance is also found in dendrites but not in the axon (axis cylinder or neurite) or axon hillock. The cell nucleus⁶³⁹ contains relatively little chromatin; it also contains a dense area called a nucleolus which contains protein and RNA. The main function of the nucleolus is the synthesis of ribosomal RNA (rRNA) and ribosomes.

Neuronal excitation

Potentials are measured in milliseconds (ms)

Graded potentials (GPs) – small changes in membrane potential, usually confined to a small part of the neuronal membrane and decreasing in magnitude from initiation site – may have local signalling role – if many stimuli arrive in close temporal association they may cause summation of GPs, which may lead to an action potential (AP: larger than a GP) - all cell membranes can transmit GPs but only excitable cells (e.g. neurones and muscle cells) can propagate an AP

Action potential (AP) – on being stimulated to a threshold level (about -55 mV) from baseline (about -70 mV or resting membrane potential [RMP]) an AP is generated which is propagated along the axon – a depolarising phase (to about +30 mV) is followed by a repolarising phase (to > -70 mV) – this latter after-hyperpolarising phase (AHP) eventually sees the return to the RMP of -70 mV – the depolarising and repolarising phases (to -55 mV) represent the absolute refractory period (no stimulus can produce another AP because voltage-gated Na⁺ channel activation gates are open during depolarisation and voltage-gated K⁺ channels are open and Na⁺ channels are inactivating during repolarisation⁶⁴⁰) whilst the AHP represents the relative refractory period (only particularly strong stimuli can lead to an AP because voltage-gated K⁺ channels remain open and voltage-gated Na⁺ channels are in a resting state)

Propagation of messages was thought to be in one direction only, from pre- to post-synaptic neurones (except for chemical feedback).⁶⁴¹ However it is now thought that action potentials propagate backwards

⁶³⁵ The Canadian psychologist, Donald Hebb introduced the idea in 1949.

⁶³⁶ The mechanism by which the size of a neuronal response increases after stimulation; enhanced by glutamate activation on NMDA receptors. Backward propagation of action potential into dendrites appears to be important in longterm potentiation.

⁶³⁷ E.g. stimulation of the visual system and, possibly, the acquisition of certain psychological capacities such as the notion of *constancy* (just because you cannot see you're mother/a ball does not mean that she/it is not present close by), an important factor in protecting the organism against excessive separation anxiety.

⁶³⁸ Neurocyte, soma, or perikaryon.

⁶³⁹ Mature red blood cells and platelets have no nucleus and hence no genome.

⁶⁴⁰ *Voltage-gated channels*: Membrane depolarisation causes Na⁺ channels to open quickly and then become inactivated. The K⁺ channels then open. Repolarisation causes Na⁺ and K⁺ channels to close.

⁶⁴¹ The terminal arborisation of the axon is known as the telodendrion, and the nerve terminals have swellings called *boutons terminaux*. The synaptic gap or cleft is about 200 Å wide. The presynaptic nerve ending contains mitochondria and vesicles, the latter being clear if they contain Ach and dense if containing monoamines.

into dendrites allowing postsynaptic depolarisation required for longterm potentiation. The postsynaptic⁶⁴² membrane is thicker than its presynaptic counterpart. Excitatory or inhibitory post-synaptic potentials (EPSP and IPSP respectively) generated at the postsynaptic membrane lead to membrane depolarisation or hyperpolarisation respectively. The cell leading, or not leading (depending on summation) to an action potential integrates EPSPs and IPSPs.

Specific membrane-bound proteins, such as synaptobrevin (neuronal) and synaptotagrin (vesicular), allow the vesicle to attach to the nerve cell membrane. Exocytosis is the process whereby the vesicle empties its contents into the synaptic gap. Exocytosis occurs in axon terminals at 'active zones' when calcium ions enter the neurone on arrival of the action potential. The vesicular membrane, recovered by endocytosis, is then reformed and the vesicle is available to be used again.

Many neurones within the CNS can generate their own activity pattern (endogenous activity involving specialised ion channels) without requiring synaptic input. There are two such patterns: pacemaker firing (regular firing) and burst firing (cluster firing).

Most neurotransmitters (NTs) are produced enzymatically within the presynaptic terminal. Neuropeptides, however, are made on ribosomes and put in vesicles in the nerve cell soma, the vesicles then being transported along the axon to the nerve terminal.

The DA system in the human brain arises in the ventral tegmental area (VTA) and substantia nigra and sends fibres along the nigrostriatal pathway (D1 + D2) to the basal ganglia, and D1 fibres (mainly) to the limbic system and then forwards and backwards over the prefrontal cortex. Fibres from the hypothalamus innervate the hypophysis (hypothalamo-pituitary tract). Psychosis might have its origins in the basal ganglia because of its richness in D2 receptors, and the ability to block D2 receptors correlates much more closely with antipsychotic drug actions than does D1 blockade. Even when medication is controlled for, the pituitary is often enlarged early in psychosis due to an increase in number and size of ACTH-producing cells. Such enlargement may precede psychosis by months in cases at very high risk for such disorders who eventually do become psychotic when compared with people at high risk who fail to progress to psychosis. (Garner *et al.*, 2005)

In aminergic pathways⁶⁴³ the cell bodies are situated in the brainstem and these neurones have close connections with the limbic system. Their efferents are unusual in that they do not have the usual nerve endings; instead they have 'nodules' along their lengths, each nodule being rather akin to an atypical synapse. Each neurone can influence up to 140,000 other neurones and bathe the cortex in their transmitter.

Prefrontal cortex (PFC)

Crucially important for pursuit of goal-directed behaviour

Lesions to orbital part of the PFC cause euphoria, overactivity, and inappropriate social behaviour

Lesions of dorsolateral part (DLPFC) are associated with apathy (lack of feeling/interest/motivation), underactivity, and impaired cognition

DLPFC dysfunction is said to occur in schizophrenia

The temporal lobe can be divided into an outer neocortical part and an older medial part. The latter consists largely of the hippocampus⁶⁴⁴ and hippocampal gyrus on the inferomedial margins of the temporal lobes.

Hippocampal formation* (HF)

Folded sheet of tissue

Includes:

*Fimbria***

Dentate gyrus

Hippocampus

Subiculum

⁶⁴² Sometimes called subsynaptic.

⁶⁴³ 5-HT, noradrenaline – only a little adrenaline is made in the CNS because of a deficiency of the appropriate enzyme.

⁶⁴⁴ 'Seahorse', *cornu Ammonis* or Ammon's horn.

*The HF has the highest proportion of corticosteroid-binding sites in the brain.

** Contains hippocampal pyramidal cell axons that join behind the hippocampal commissure to form the fornix.

The hippocampus is divided into sectors (CA1-4) on the basis of cellular architecture⁶⁴⁵. The HF fold consists of three-layered old cortex that projects into the lateral ventricle; the HF is continuous with the six layers of the entorhinal neocortex. The change from 3 to 6 layers occurs at the subiculum. Entorhinal and perirhinal cortices meet anteriorly. The entorhinal cortex forms part of the parahippocampal gyrus posteriorly. A loop is completed as follows: dentate gyrus granule cells → CA3 pyramidal cells → CA1 pyramidal cells → subiculum → entorhinal cortex. Pyramidal and polymorphic cell axons form the alveus that runs along the ventricular hippocampal surface. These develop into fimbriae, crura of fornix, and body of fornix. The fornix ends in the hypothalamic mamillary bodies. The fornix, apart from cholinergic speto-hippocampal fibres, is an output system.

The HF processes incoming information and acts as a short-term memory store. The hippocampus is important for declarative memory, i.e. for remembering facts, experiences and information about events⁶⁴⁶. Long-term memory is mainly in the temporal lobe.

The medial temporal lobes

Right-sided damage/dysfunction – problems with acquisition of new **spatial** information

Left-sided damage/dysfunction - problems with learning and retaining new **verbal** information

The planum temporale is a triangular plane lying on the superior and posterior surface of the temporal lobe (just behind Heschl's gyrus) and, on the left side, forms part of the biological substrate for language⁶⁴⁷. The left planum temporale is bigger than the right one in two-thirds of all brains. Work on animals suggest that direct exposure to glucocorticoids may lead to loss of pyramidal neurones and dendritic branching in the hippocampus.(Woolley ea, 1990)

The dentate gyrus of the hippocampus produces new neurones from dividing progenitor cells in adult animals, including humans⁶⁴⁸. Psychological stress decreases the rate of neurone formation. Stress plus corticosteroids may cause cell death. Various antidepressant drugs, ECT, and lithium increase neurogenesis⁶⁴⁹ in rats.(e.g. Malberg ea, 2000) Tianeptine may preserve neurogenesis potential in face of stress, and ECT prevents steroid-induced reductions in new neurone formation in animals.(Steele & Reid, 2004)

The hippocampus in depression (Whale, 2008)

Hippocampal shrinkage occurs whilst depression remains untreated

Hippocampus is sensitive to BDNF⁶⁵⁰ – depression and stress decrease BDNF

Neurogenesis⁶⁵¹ is increased by BDNF, antidepressants, oestrogens, exercise, sexual activity, a stimulating environment

Neurogenesis is decreased by ageing, stress, corticosteroids, and NMDA (glutamate)

The occipitotemporal (fusiform) gyrus lies on the ventromedial surface of the temporal and occipital lobes. It is important for face recognition. It appears to be dysfunctional in prosopagnosia and perhaps in delusional misidentification syndromes. There is increasing evidence that patients with schizophrenia may have deficits in face processing, including those patients at first hospitalisation.(Lee ea, 2002)

⁶⁴⁵ The CA1 subfield may be differentially targeted in schizophrenia.(Schobel ea, 2009)

⁶⁴⁶ As distinct from procedural memory, memory for skills.

⁶⁴⁷ This area contains the auditory association cortex, i.e. Wernicke's area.

⁶⁴⁸ Apart from this, brain-injured patients may compensate for their difficulties when remaining cortex takes over from damaged areas. Magavi ea (2000), working with adult mice, found that hippocampal, subventricular, and even neocortical neurones could be induced to divide to produce daughter neurones and that these could then form connections with distant structures.

⁶⁴⁹ It is disputed as to whether neuro-regeneration of neurogenesis is the correct term. It now appears feasible to grow neurones from non-neuronal adult cells *in vitro*.

⁶⁵⁰ The gene for **BDNF** is at 11p14. 5-HT and norepinephrine increase BDNF synthesis via cAMP. **Neurokinins** (e.g. substance P) co-transmit with 5-HT and norepinephrine. There is a suggestion that NK1 antagonism is antidepressant. **Δ Fos B** is linked to learned helplessness in rats. There is evidence that life events must occur before increased cortisol occurs in depression.

⁶⁵¹ The adult brain can form new neurones only in the dentate component of the hippocampus and in part of the olfactory bulb.

Amygdala

A forebrain structure

Part of limbic system

On roof of temporal horn of lateral ventricle

At inferior end of caudate nucleus⁶⁵²

Adjacent to the uncus

Divided into various nuclei⁶⁵³

Entorhinal cortex and hippocampus have role in regulating responses of amygdala

Amygdala enhances storage of emotionally important memories in medial temporal lobe

Amygdala responses inhibited by medial prefrontal cortex when they cease to be relevant

Lesions of the amygdala may cause fearfulness and suspiciousness. Infusion of CRF into the amygdala of animals leads to behaviour reminiscent of anxiety, a response that may mimic stress-induced anxiety in the human. The CRH1/CRF1 receptor may modulate the anxiety-inducing effects of CRH (Holsboer, 1999) and a variant of the CRH1 receptor gene (TAT haplotype) might protect against the development of adult depression in women following childhood maltreatment. (Polanczyk et al., 2009) With the hippocampus, the amygdala is probably very important for learning and memory; it may also have a role in such activities as facial perception and recognition (as well as deciding how approachable/trustworthy a face appears to be)⁶⁵⁴, and the expression of aggression. Recognition of emotion in faces (especially fear and disgust⁶⁵⁵) is impaired in schizophrenia (no benefit accrued from increased emotional intensity), with a tendency to view neutral cues as negatively valenced. (Kohler et al., 2003) Paradiso et al., (2003) in a PET study, found that, unlike control subjects, when schizophrenics consciously evaluated unpleasant images they did not activate the amygdala, although they correctly rated them as unpleasant; also, they did not activate areas of the prefrontal cortex normally employed to recognise images as pleasant and were unable to recognise them as such; areas of reduced cerebral blood flow were widely distributed and included subcortical areas such as thalamus and cerebellum.

According to Parkin, (1987) amygdectomy alone does not cause amnesia. It is rare to find cases with discrete bilateral amygdala destruction, but it can occur, e.g. with lipoid proteinosis (Urbach-Wiethe disease, an autosomal recessive disorder involving skin, pharynx, and larynx). According to Liddle, (2001, p. 45) the amygdala responds to external imperatives by mobilising a fight or flight response at the expense of concurrent cognition, whereas the hippocampus is involved in a more reflective evaluation of current circumstances. According to Cras, (2002) the amygdala is important in the association of a particular emotion with a current experience. Contextual learning in rats seems to depend on an intact connection between amygdala and hippocampus.⁶⁵⁶ (Kim & Fanselow, 1992)

The *stria terminalis* is composed chiefly of fibres running from amygdala to hypothalamus and adjacent mesial basal forebrain. Scattered along the *stria terminalis* are patches of grey matter known as the *bed nucleus*, the largest part of which is in the mesial basal forebrain beside the lateral septal nuclei in the inferior septum pellucidum.

⁶⁵² The amygdala is found where the tail of the caudate nucleus meets the most anterior part of the hippocampus/parahippocampus.

⁶⁵³ Lateral, basolateral, basomedial, central (where vasopressin/oxytocin balance may influence set-point for anxiety response and activation of autonomic nervous system), medial, and cortical nuclei and amygdalocortical transition area.

⁶⁵⁴ A person with bilateral amygdala lesions can recognise who owns a face but not the **facial expression of fear**; this structure is therefore important in processing stimuli related to fear.

⁶⁵⁵ **Disgust** is taught by parents to ward off ingestion of contaminated materials but it may be involved in a number of psychiatric disorders. There may be impaired disgust recognition in schizophrenia and in Huntington's disease. Spider phobia is reported as being linked to disgust rather than fear. Disgust (leading to vasovagal syncope) is an important but not consistent finding in blood-injection-injury phobia. Other theoretical connections may be with contamination-based OCD, social phobia, eating disorders, sexual dysfunction, body dysmorphic disorder, coprophagia, and depression. (Phillips et al., 1998; Olatunji & McKay, 2007)

⁶⁵⁶ Normally tone + electric shock in a cage → associates cage with shock (i.e. fear occurs on being near cage: *contextual fear conditioning*), but after damage to amygdala tone only → fear (but not cage → fear).

Cavum septum pellucidum

Atypical space lying between the two layers of the septum pellucidum
Does not necessarily signify abnormal function

The Papez⁶⁵⁷ circuit can be described as follows. The mamillary body sends fibres via the mamillo-thalamic tract to anterior thalamic nuclei that then send fibres to the cingulate cortex and cingulum.⁶⁵⁸ The latter project to entorhinal (anterior part of parahippocampal gyrus with wart-like lumpy surface) and subicular cortices (medial temporal lobe). Entorhinal fibres pass via the perforant pathway to the dentate gyrus. Fibres from the latter project to hippocampal pyramidal cells. Hippocampal fibres and fibres running from the subicular cortex run in the fornix; they run backwards and upwards, arch up under the splenium and run forwards under the corpus callosum ('firm body' – connects homotypic regions of the two cerebral hemispheres), then turn downwards (as the columns of the fornix) to run through the hypothalamus, and end up in the mamillary body.⁶⁵⁹

Cerebral dominance is a too simplified notion. The hemispheres are functionally asymmetrical (lateralisation). Dominance refers to language and preferred hand, foot and eye use. The nondominant hemisphere is responsible for visuospatial function.

CNS control of visuospatial function

Information from visual cortex to temporal (ventral) or parietal (dorsal) cortex travels in 2 streams

*Ventral stream*⁶⁶⁰ – information linked to semantic data – 'what is it?'

*Dorsal stream*⁶⁶¹ – allows link between visual data and spatial position/orientation – 'where is it?'

Frontal eye fields – allows one to direct attention towards a target in the visual field

The thalamus⁶⁶², wherein sensory and motor information is relayed, consists of a number of nuclei,

Nuclei of thalamus

Dorsomedial (information received from [IF] the prefrontal cortex [PFC] and hypothalamus and sent to [ST] the PFC; a sense of dreadful foreboding follows stimulation)

Dorsolateral (IF cingulate gyrus and parietal cortex and ST the same areas)

Anterior (IF mamillothalamic tract and ST cingulate gyrus; a limbic structure)

Ventral anterior and ventral lateral (IF cerebellum and basal ganglia and ST premotor and motor cortices)

Posterolateral (IF occipital cortex and ST parietal cortex)

Medial and lateral ventroposterior (relays sensory information)

Intralaminar (part of reticular formation; IF from midbrain, PFC and motor area and ST basal ganglia)

Pulvinar (IF non-frontal cerebral cortex and ST to visual cortex)

Medial geniculate body (IF lateral lemniscus and ST primary auditory cortex)

Lateral geniculate body (IF optic tract and ST primary visual cortex)

⁶⁵⁷ The term *grand lobe limbique* (limbic lobe) was coined by Paul Broca in 1878. James W Papez of Cornell University wrote his paper in 1937. Papez's ideas were expanded on during the 1950s by the US physician and neuroscientist Paul MacLean (1913-2007) who considered that we had three 'brains' (*triune brain*): reptilian complex, limbic system, and neocortex. The list of constituents of the limbic system has not remained constant over the years.

⁶⁵⁸ The **cingulate** is 'an amplifier and filter, interconnecting the emotional and cognitive components' of mental life. (Devinsky et al, 1995) It has an important role in the emotional aspect of pain. The dorsal anterior cingulate cortex is involved in allocation of attention and monitoring for errors.

⁶⁵⁹ Put more simply, this circuit can be expressed thus: *mamillary body* → *ant. thalamus* → *cingulum* → *medial temporal lobe* → *dentate gyrus* → *hippocampus* → *fornix* → *mamillary body*.

⁶⁶⁰ This goes from occipital lobe to temporal lobe and especially allows recognition of people and objects.

⁶⁶¹ This goes from occipital lobe to parietal lobe and is important for visual guidance of action. Depressed patients show less engagement (as measured by magnetoencephalography and self-report) of this stream when watching pictures than do controls although, like controls, engagement is greater for emotional pictures than for neutral pictures. (Moratti et al, 2008) **Balint's syndrome** (bilateral dorsal stream lesioning) includes simultanagnosia (inability to discern > 1 item in visual scene simultaneously), optic ataxia (difficulty reaching for an object that is seen), and oculomotor dyspraxia (inaccurate directing of eye movements).

⁶⁶² Gk., inner chamber.

The thalamus acts as pacemaker by exerting rhythmic control over large groups of cortical neurones. Destruction of the thalamus abolishes rhythmic activity in the cortex. According to Andreasen, (2003) all experiences and perceptions flow into the thalamus which acts as a filter that allows suppression of irrelevancies and selection of important items. The pulvinar is important for connecting visual and auditory information.

The hypothalamus consists of preoptic (gonadotrophic hormone production; sleep generation), supraoptic (anterior, paraventricular, and suprachiasmatic components: parasympathetic nervous system; vasopressin [arginine vasopressin, AVP, antidiuretic hormone, ADH] and oxytocin production), mamillary (limbic area involved in memory), tuberal (ventromedial and dorsomedial components: the first component is involved in hunger and satiety, and the latter subnucleus is important for emotion such that rage occurs if it is destroyed), arcuate (fibres from here carry neurohormones to the adenohypophysis: the arcuate nucleus is outside the blood-brain barrier and has insulin, ghrelin and leptin receptors), and posterior (sympathetic nervous system) nuclei. The various hypothalamic releasing hormones either stimulate the release (e.g. corticotrophin [corticotropin⁶⁶³] releasing hormone [CRH] causes release of ACTH) or inhibits the release (e.g. somatostatin and dopamine inhibit growth hormone and prolactin release respectively) of hypophyseal hormones. However, hypothalamic peptides also act as neurotransmitters elsewhere in the brain, e.g. CRH has an activating effect on the locus coeruleus leading to noradrenaline release and this noradrenaline then activates CRH from the hypothalamus and the amygdala, a property (reciprocal stimulation) that may be important in the insomnia and anxiety associated with clinical depression.

The epithalamus is a collective term for the stria medullaris, the pineal gland, and the medial and lateral habenular nuclei. The habenular complex consists of relay nuclei that link limbic forebrain to midbrain and brain stem nuclei and may be reduced in size and neuronal cell number in depression. (Ranft ea, 2010)

The subthalamus⁶⁶⁴ is a complex set of nuclei important for motor function.

The striatum has a medial part (caudate) and lateral part (putamen) which are separated by perforating fibres of the internal capsule (see box).

Striatum consists of –
Caudate nucleus ('tail') and putamen ('stone')
Lentiform nucleus consists of –
Putamen and globus pallidus ('pale globe')

The C-shaped caudate nucleus is adjacent to the lateral ventricle and bounded by the internal capsule. It is divided into a head (in the frontal lobe), body, and tail (in the temporal lobe).

The pyramidal system (corticospinal tract) is important for the execution and control of skilled voluntary movements. The extrapyramidal system (with cerebellar inputs) is important for muscle tone distribution and posture maintenance. The cerebellum, in receipt of 'command' and 'response' information, compares both and corrects motor performance by its influence on the cortex via the basal ganglia or muscles via the reticular formation.

The anatomy of the stretch reflex is as follows. An intrafusal muscle fibre has two contractile ends and a central membranous, stretchable component. Ia afferent nerve fibres wind around the membranous part of the intrafusal muscle fibre. Impulses from these nerve fibres travel via their nerve cell bodies in the posterior root ganglia to synapse with the big alpha-motor neurones of the ventral horn of the spinal cord, the latter sending thick efferent fibres called A α fibres to motor endplates of striated muscle fibres. Smaller gamma-motor neuronal bodies lie close to the α -motor neuronal bodies in the cord and send thin A γ -fibres to the contractile ends of the intrafusal muscle fibre. Descending fibres from higher centres synapse with both alpha-motor neurones and gamma-motor neurones. Thus, nerve cells in higher brain centres influence the contractile state of muscle by acting on α -motor neurones or via the gamma loop. Put simply, gamma-motor neurones cause the ends of the muscle spindle to contract, thereby stretching the central membranous part; impulses then travel to the alpha-motor neurone via afferent nerve fibres.

⁶⁶³ CRH is also produced by the placenta during pregnancy (pCRH) and increased levels of pCRH in mid-pregnancy may be predictive of postpartum depression. (Yim ea, 2009) Cortisol suppresses hypothalamic CRH release but stimulates pCRH release.

⁶⁶⁴ Thalamus ventralis. A CVA (infarct or bleed) involving the subthalamic nucleus is associated with contralateral **hemiballismus** (wild swinging movements) which is treated with antipsychotic drugs. Hemiballismus usually resolves over some weeks.

That part of the cerebral cortex that is responsible for integrating information coming from many different sources is known as the association cortex, the sensory association cortex processing complex aspects of sensory stimuli and the multimodal association cortex integrating information from the different senses with motivations and goals.

Functional divisions of cerebral cortex

Primary – unimodal (sensory or motor)

Association – multimodal (receiving input from many areas) – frontal (executive, including impulse inhibition); limbic (memory, emotion); and sensory (integration of sensory input, including temporal, parietal, and occipital components) areas

OR

Idiotypic (primary) – such as primary visual, auditory, and motor areas

High-order (heteromodal) – such as motor association area and frontal eye fields

Modality-specific (unimodal) - such as visual association cortex

Paralimbic - orbitofrontal (ventromedial) cortex, temporal pole, insula, cingulate cortex, and parahippocampal cortex, (coming together of cognitive, emotional, and visceral inputs)

Cortical network regions

(Transmodal cortical areas that control different aspects of cognition)

Executive function/working memory – Lateral prefrontal and (?) inferior parietal cortex

Language – including Broca's and Wernicke's areas

Spatial awareness – frontal eye fields and posterior parietal area

Memory and emotion – amygdala and hippocampus/entorhinal area

Face/object recognition – temporal (polar and mid) cortex

*Fronto-subcortical networks*⁶⁶⁵

(Involved in cognition, behaviour, and movement)

Somatic motor – starts in supplementary motor area

Oculomotor – starts in frontal eye fields

Dorsolateral prefrontal – executive function

Orbitofrontal – joins the monitoring role of prefrontal cortex with limbic system

Anterior cingulate – concerns motivated behaviour

Executive function (EF) is not simply something that happens in the prefrontal cortex. Subcortical connections of the latter to basal ganglia (caudate, nucleus accumbens, globus pallidus), thalamus, and cerebellum are also part of the EF system and damage to any of them or their interconnections can interfere with EF.

The pathway allowing light signals to influence the pineal gland appears to be as follows: retina to suprachiasmatic nucleus, to paraventricular nucleus to synapses in the spinal cord, and then via sympathetic outflow to superior cervical ganglion, and thence via the *nervi canarii* to the pineal gland, i.e. a circuitous, multi-synaptic pathway.

Saccadic eye movements (i.e. visual search) involve a projection from the occipito-parietal cortex to the frontal eye fields (in the frontal lobe).

Gender differences in brain development have attracted increasing attention.(Castle & Murray, 2002)

Testosterone produced by the embryonic testis may slow brain development. It has been suggested that the male brain is slower than the female brain to lay down myelin and form connections between neurones.

The effect of such slowing may be chiefly left-sided. This may render male brains more vulnerable to insults, e.g. low birth weight may be more likely to lead to haemorrhage in the area of the cerebral ventricles if the sex is male, and 12-year-olds with minor neurological dysfunction are more often male and have suffered early environmental insult such as hypoxia. Male brains on average are larger than female

⁶⁶⁵ Frontal cortex → striatum → globus pallidus/substantia nigra → thalamus → frontal cortex. **Fronto-subcortical dementia** refers to the co-existence of frontal and subcortical symptoms due to disruption of fronto-subcortical circuits (e.g. in some cases of vascular dementia): dorsolateral prefrontal cortex-subcortex (executive dysfunction), orbitofrontal-subcortex (disinhibition), and medio-frontal/cingulate-subcortex (apathy and depression).

brains. Other differences include a larger preoptic nucleus (of the hypothalamus) and greater asymmetry of the planum temporale in males. Females may have greater bilateral representation of cortical functions than males. Ageing female brains may lose a greater amount of parietal, thalamic and hippocampal volumes than is the case in males, the opposite occurring in terms of whole-brain, frontal and temporal volumes. According to Andreasen,(2003) lose grey matter earlier and faster than do women. Males may have more D2 receptors to begin with but by mid-life end up with relatively less than females.

Kindling (Goddard & Morrell, 1971) is that process in which increasing behavioural or convulsive responses occur to repetition of the same stimulus over time. Carbamazepine is highly effective in inhibiting an amygdala-kindled compared to cortical-kindled focus. Goddard & Morrell,(1971) who described the phenomenon, indicated that limbic system structures, particularly the amygdala, were most susceptible to kindling. In animals, once seizures develop in response to repeated amygdala stimulation, they can again be evoked months to years later even in the absence of further stimulation. Cats who kill rats will cease to do this if they are amygdala-kindled. Pharmacological kindling can be performed with the local anaesthetic lidocaine. Repeated giving of lidocaine causes the development of seizures and abnormal behaviour that follow a kindling-like time course. Marked increases in irritability and aggression are seen in that animals show repeated lidocaine-induced limbic seizures. To distinguish it from ‘electrophysiological kindling’ (increased responsivity to repeated stimulation of the brain), when behavioural effects occur without seizures, the phenomenon is styled ‘behavioural sensitisation’; e.g. increasing responsivity to repeated administration of the same dose of a stimulant such as cocaine. The latter is not as long lived as electrical kindling. Post (1992) has speculated on how environmental stress may induce genetic and other neurobiological changes, especially in the acute phase of affective illness, which might lead to a cascade of events that allows the illness to become autonomous of the ‘mental’ experiences of the individual. The idea that prolonged glucocorticoid secretion may cause memory and cognitive deficits by being toxic to hippocampal neurones is based mainly on animal work.(O’Brien, 1997) The concept of mass action or equipotentiality holds that learned behaviour is diffusely organised in the brain, and that it is the extent of a lesion rather than its site that determines loss of function, as applies to intellectual loss in dementia. Also, it should be noted, slowly expanding/spreading lesions/disorders are compatible with adaptive change and retention of ability, e.g. the very thin cortex of the child with hydrocephalus is still compatible with retention of premorbid IQ because of the slow progression of cortical thinning. Also, the functions of one cortical area may be undertaken by another area, and there is probably some cortical reserve that can be called on in the event of damage. There is evidence that dendritic growth continues into old age. There is also evidence that columns of cortical cells are functionally capable of independent and highly specialised function and action and can escape damage to independent and adjacent columns.

The chief consumer of body *glucose* is the brain – the brain of a 70 kg man needs 1 mg/kg bodyweight/minute (100 g/24 hrs). Half of all glucose made in the liver is consumed by the brain where the derived energy goes to make the ATP that is needed to guarantee the trans-axonal membrane potential difference. The brain’s glucose uptake is obligatory and non-insulin dependent.

Neurochemistry, psychopharmacology and neuropharmacology

Doctors should consider stopping treatments that have not benefited the patient despite being taken for long enough and in adequate dosage.

Neuropharmacology is the study of the effect of drugs on nervous tissue, whereas psychopharmacology is the study of drug effects on behaviour.

The classical form of neurotransmission involves transmission of a message by chemical messenger (neurotransmitter) from one nerve cell (neurone⁶⁶⁶) to another across a cleft, potential space, or synapse. *Volume transmission*, on the other hand, is due to diffusion of a neurotransmitter (NT) to sites distant from the neurone. A small number of synapses do not use neurotransmitters but involve the direct flow of small molecules and ions from the cytoplasm of one cell to the adjacent cytoplasm of another cell through channels called *gap junctions*.

Receptors⁶⁶⁷ and enzymes are manufactured in the cell body (soma) and then transported to the cell periphery. The effect of activating a postsynaptic receptor largely depends on the location of where the

⁶⁶⁶ Neuron in USA.

⁶⁶⁷ Receptors are usually large protein or glycoprotein molecules in the cellular membrane, cytoplasm, or nucleus.

receptor is on the postsynaptic neurone. Activation of an ion channel-linked receptor located near the axon hillock, the site of generation of the action potential is generated, will have a far greater effect than activation of a similar receptor on a dendritic spine. In the latter case, activation of many receptors may be necessary to change the cell's activity. Because G-protein-linked receptors activate a cascade of second messengers, the effects of their activation is not so dependent on location.

Ion channels

These may be rested, activated, or inactivated

Rested = closed but can be opened if stimulated

Activated = open

Inactivated = closed and cannot be opened if stimulated

The majority of ion channels are inactivated and remain like this until they open when a specific signal dictates their opening – this phenomenon is called *gating*

Gating is governed by changes in the membrane environment

Voltage-gated ion channels: open in response to changes in membrane potential⁶⁶⁸

Ligand-gated ion channels: open in response to changes in concentration of a neurotransmitter molecule

Most receptors are in the cell's surface membrane and are divided into ionotropic (or ligand-gated ion) and metabotropic receptors. Intracellular receptors interact with chemicals like steroids⁶⁶⁹ and thyroid hormones.

Class I (ionotropic) receptors are ligand-gated ionic channels. Activation leads to a rapid and transient increase in membrane permeability and inhibition (e.g. GABA A receptors are inhibitory⁶⁷⁰) or activation (e.g. cholinergic nicotinic receptors) of the postsynaptic membrane. The receptor consists of a number of subunits surrounding a channel in the membrane. When an agonist binds to the receptor the channel opens. Normally, there is an excess and a deficit of potassium and sodium inside cells respectively. At excitatory ionotropic receptors neurotransmitter binding opens the ion channel and an opened channel allows potassium ions to move outward and sodium ions to move inward, with depolarisation of the transmembrane potential and the generation of excitatory postsynaptic potential (EPP). At inhibitory ionotropic receptors neurotransmitter binding causes the opening of chloride channels with the influx of chloride ions with membrane hyperpolarisation and the formation of an inhibitory postsynaptic potential (IPP).

Ionotropic receptors

- Neurotransmitter + excitatory receptor → K⁺ efflux + Na⁺ influx → depolarised membrane + EPP
- Neurotransmitter + inhibitory receptor → Cl⁻ influx → hyperpolarised membrane + IPP

The GABA A (GABA_A) complex consists of a ring of transmembrane proteins. The latter are arranged in 5 groups designated α , β , γ , δ , and ρ . Benzodiazepines (BZDs) are agonists at α subunits, GABA acting at β subunits. α , β , and γ act together to form the ω -1 or benzodiazepine receptor. Brain BZD receptors in the brain are divided into BZ1 (type 1, omega 1) and BZ2 (type 2, omega 2). Omega 3 receptors are common in the periphery. Zaleplon and zolpidem bind selectively to GABA A receptors containing alpha-1 subunits. GABA A receptors with alpha-1 subunits may mediate sedation, amnesia and anticonvulsant activity.

Those containing alpha-2 and alpha-3 subunits may mediate anxiolysis and muscle relaxation.

Class II (metabotropic) receptors give a slower response. G-proteins bind to the intracellular part of the receptor and are involved in second messenger activation (such a division of G-proteins is now known to be simplistic because G-proteins can interact with more than one effector system with varying results; also,

⁶⁶⁸ On arrival of an action potential at the nerve terminal voltage-gated Ca⁺⁺ channels are involved in the initial conversion of the electrical message into chemical transmission.

⁶⁶⁹ Ligands that are lipid soluble do not require secondary messengers. Once their receptors in the cytoplasm are activated they enter the nucleus, bind with DNA, and directly change gene expression.

⁶⁷⁰ However, GABA-A receptors are excitatory in (a) early development (because of high levels of chloride within cells) and (b) in some mature synapses (especially some projecting into initial segments of cortical pyramidal neurones). (Szabadics et al, 2006)

there are a number of families of G-proteins, each with a number of subunits with various tissue distributions, receptor agonists and known or unknown effectors; basically, G-proteins⁶⁷¹ have 3 different subunits – it is the α subunit that determines which receptor a G-protein complex interacts with and the type of effector system that will be modified; $G_{\alpha s}$ stimulates and $G_{\alpha i}$ inhibits adenylate cyclase – $G_{\alpha o}$ modulate voltage-sensitive calcium channels and phospholipase C whereas $G_{\alpha olf}$, found in the nasal mucosal neurones, are involving in transducing signals derived from olfactory receptors).

The receptor consists of long peptide chains with a number of subunits within the membrane and a long intracellular loop that binds the G-protein. Various second messengers may then be activated or inhibited, including adenylate cyclase (producing cAMP, leading to phosphorylation of other enzymes), activation of phosphoinositide turnover and calcium release, the conversion of arachidonic acids to prostaglandins, leukotrienes and other active compounds, and indirect activation of ion channels.

A neurotransmitter (NT), such as acetylcholine (ACh)⁶⁷², is a substance secreted by a neurone (nerve cell) that acts on a target neurone. A NT must be made in a neurone, be present in the presynaptic neurone, and be released on depolarisation in physiologically significant amounts. When given exogenously as a drug it should mimic the actions of the endogenous NT. Also, a mechanism should exist in the neurone or the synaptic cleft for its removal or deactivation.

The term neurohormone (e.g. CRF) refers to neuronal peptide⁶⁷³ secretions that directly enter the blood stream. These act on other neurones, as do neurotransmitters. A neuromodulator (e.g. steroids; CRF from lymphocytes) is a substance that influences neuronal activity and originates from non-synaptic sites. Neuromodulation refers to a situation whereby an NT's actions, among others, alter the responsiveness of postsynaptic cells to the effects of other synaptic inputs. Neuromodulatory NTs act, not by directly affecting neuronal firing, but by modifying neuronal excitability, so that responses to other NTs are altered (Cf. allosteric modulation below). An example is the action of BZDs on the GABA receptors (see below). (Dolan & Grasby, 1994) Neuromediators are postsynaptic compounds (e.g. cAMP) that participate in the generation of postsynaptic responses. Because of the difficulty in practice of fulfilling the criteria for neurotransmitter, neuromodulator and so on, a general term for all substances involved in chemical transmission has been proposed: neuroregulators. (Iritani, 2002)

In contrast to the classical but slower genomic (gene expression) mechanisms of steroid activity, neuroactive steroids⁶⁷⁴ regulate neuronal function by influencing neuronal excitability (non-genomic mechanisms via ligand-gated ion channel receptors). DHEA, which is metabolised to androstenedione (the latter is converted to androgens and oestrogens), may cause maculinisation, hirsutism, and changes in the voice. In humans, DHEA may improve mood⁶⁷⁵ and the symptoms of schizophrenia. Negative affect in healthy girls may relate to high testosterone and cortisol levels and low levels of DHEA. (Susman et al, 1991) *Allosteric*⁶⁷⁶ modulation refers to the situation where there are two sites on a receptor and only when a neurotransmitter (NT) acts on its site can another chemical cause an effect. In other words, the action is an indirect one. The allosteric modulator can block or amplify the actions of the primary NT. In the absence of the primary NT the second chemical will have no particular effect. An example is seen at the GABA receptor where benzodiazepines, barbiturates and anticonvulsants may act allosterically.

A different phenomenon is *co-transmission*. In this, each of 2 NTs work somewhat independently of each other, but can have additive effects if working together, e.g. glutamate and glycine at some glutamate receptors.

A *ligand* is a substance that binds with receptors. In research these are usually labelled with a radioactive isotope.

⁶⁷¹ Alfred Gilman and Martin Rodbell received Nobel Prize in 1994 for discovery of G-proteins.

⁶⁷² Discovered in ergot in 1914 by Henry Hallett Dale (1875-1961), a London physiologist. Called *Vagustoff* (vagus material) by Otto Loewi (1873-1961 – Nobel Prize, 1936), professor of pharmacology at Graz, after it was found in heart muscle in 1921. Eccrine sweat gland are innervated by cholinergic sympathetic fibres and those of the palms and soles are activated by emotion and this assists grip. In the CNS, **acetylcholine-containing (cholinergic) neurones** are found in the nucleus basalis of Meynert (which project diffusely to neocortex), septum and diagonal band of Broca (projecting to hippocampus, hypothalamus and amygdala), and (as interneurons) in the basal ganglia. Choline, the precursor of acetylcholine, is derived from recycled synaptic ACh and dietary phosphatidylcholine.

⁶⁷³ A peptide is a number of amino acids strung together by peptide bonds. A neuropeptide or neuroactive peptide is a peptide with neurophysiological activity.

⁶⁷⁴ E.g. dehydroepiandrosterone or DHEA and its sulphated form DHEA-S.

⁶⁷⁵ E.g. in elderly, those with SLE, dysthymics, major depression, and non-major depression in association with HIV/AIDS.

⁶⁷⁶ Allosterically simply means 'at another site'.

The number of putative NTs is increasing. The main NTs of importance to psychiatry are catecholamines (inhibitory at synapses, i.e. inhibit spontaneous firing of receptive cells; noradrenaline and dopamine – there is a benzene ring with two attached hydroxyl groups [catechol nucleus] and opposing side chain of ethylamine or one of its derivatives), indoleamines (inhibitory except for limbic cortex; 5-HT), neutral amino acids (inhibitory; GABA), peptides (inhibitory, except hippocampus; endorphins), choline esters (excitatory; Ach), and dicarboxylic amino acids (excitatory; l-glutamic acid). Other putative NTs include cholecystokinin⁶⁷⁷ (CCK, produced by mucosal endocrine cells of proximal small intestine), substance P, and vasoactive intestinal (poly-) peptide (VIP).

Pharmacological terms

Adverse drug reaction (ADR): a reaction that is harmful and unintended and occurs with doses used in man for prophylaxis, diagnosis or treatment of disease or modification of physiological function.

Agonist: compound acting on receptor to produce similar effects to natural ligand.

Agonist spectrum: if we imagine the antagonist, which has no intrinsic activity, in the centre, then the strength of agonist activity increases through partial agonist to (full) agonist, and the strength of inverse agonist (having effects opposite to an agonist) activity increases through partial inverse agonist to (full) inverse agonist. An antagonist reverses the actions of all 4 types of agonist. For example, in the case of a ligand-gated channel the resting state is one of partially opened channel, but full agonists open it fully. Partial agonists open it a little less fully, inverse agonists close it fully, partial inverse agonists almost close it, and the antagonist brings it back to its resting state in all cases. (Stahl, 2000) Partial agonists have low intrinsic activity but high affinity. They can therefore inhibit agonists with high intrinsic activity. Net effect is antagonism of agonists. One of aripiprazole's actions is as a partial DA agonist.

Amine: organic compound containing the amino group (-NH₂).

Antagonist: compound that blocks receptors, thereby preventing agonist or inverse agonist from eliciting a physiological response. It should have no biological activity of its own, e.g. flumazenil.

Anticholinergic load: the summed anticholinergic activity of all drugs being taken by a patient. Taking the anticholinergic strength of atropine as 1, the anticholinergic strength of the following drugs is instructive: propranolol, 0.00; ranitidine, 0.22; digoxin, 0.25; theophylline, 0.44; prednisolone, 0.55; and cimetidine, 0.86! (Tune ea, 1992) Even warfarin has anticholinergic effects. Serum anticholinergic load in schizophrenia may cause cognitive dysfunction and diminish the effects of cognitive training efforts. (Vinogradov ea, 2009)

Autoreceptor: a specific receptor on NT-producing cell bodies or presynaptic terminals, stimulation of which inhibits NT release, e.g. D2 and 5-HT1 autoreceptors. In the central noradrenergic system, alpha-2-adrenoceptors act as autoreceptors. Agonists acting on 5-HT1A (somatodendritic) receptors in the raphe nuclei inhibit raphe neurone firing, but agonists acting on hippocampal 5-HT1A (postsynaptic) receptors produce serotonin-like effects. A common functional variant (C[-1019]G) variant in the human 5-HT1A gene (HTR1A) was shown to be associated with significantly decreased threat-related amygdala reactivity. (Fakra ea, 2009)

Bioavailability (F): That fraction of an administered drug that reaches the systemic circulation. In the case of oral drugs bioavailability is the fractional absorption of oral compared to intravenous drug. Sublingual absorption (e.g. oro-dispersible olanzapine or risperidone) is rapid because first-pass metabolism is avoided since the mouth drains into the superior vena cava and thus avoids the liver.

Dale's law: a defunct belief that neurones only use one transmitter at all its terminals. (see neuropeptides)

Desmopressin (DDAVP): an analogue of antidiuretic hormone; used orally or as a nasal spray to treat enuresis, with onset of action measured in several days. It may cause nasal dryness or irritation and headache. Side effects are uncommon if electrolyte regulation is normal. As with TCAs, few patients become completely dry, and relapse follows DDAVP discontinuation. Desmopressin has become popular because of the potential toxicity of TCAs.

Dichlorodiphenyltrichloroethane (DDT): use of this highly fat-soluble disinfectant is restricted nowadays because of potential toxicity including facial palsy, dizziness, tremor, delirium, convulsions and, with

⁶⁷⁷ The effects of cholecystokinin, glucagon, TRH, and somatostatin on appetite (inhibition) are probably mediated by the vagus nerve. Bombesin, a gastric peptide, inhibits feeding independent of the vagus nerve. Calcitonin and gastrin-releasing peptide also inhibit feeding.

chronic exposure, e.g. in malaria-control workers, poor neurobehavioural function. (van Wendel *de Joode* et al, 2001)

Down-regulation: 'desensitisation' of receptors; after prolonged stimulation by agonists the cell becomes refractory to further stimulation; various explanations include chemical changes and hiding receptors from ligands by withdrawing them into the cell. (Cf. up-regulation) β -arrestins interfere in G protein receptor interaction leading to desensitisation of G protein-mediated receptor signalling, and β -arrestin-1 levels are elevated in rat brain by antidepressant drugs. (Avissar et al, 2004)

Elimination half-life: the time required for the blood concentration of a drug to decline by 50% - largely determined by rates of hepatic metabolism and renal excretion.

Flavonoids: grapefruit juice contains members of this chemical family, e.g. naringin and quercetin. They inhibit P450-dependent hepatic isoenzymes (CYP1A2 and CYP3A3/4/5), therefore, for example, increasing peak plasma midazolam levels by 56%. Intravenous midazolam levels are not affected because the liver is bypassed. This phenomenon has implications for other drugs (BZDs, SSRIs, antihistamines, carbamazepine, calcium channel blockers, certain anti-arrhythmics, erythromycin⁶⁷⁸, ketoconazole, cyclosporine) and hormonal agents (cortisol, ethinyloestradiol, tamoxifen) that are partly or completely metabolised by such enzymes. CYP1A2 is induced by cigarette smoke, modafinil and char grilled meat whereas CYP3A4 is induced by St John's Wort, barbiturates and carbamazepine.

Half-life of a drug: time required for its concentration to fall in plasma by 50%; the quicker is metabolism and elimination, the shorter the half-life.

Heteroreceptor: Some presynaptic receptors are specific for a neurotransmitter (NT) other than the nerve cell's own NT, allowing for modulation of release of one NT by another, e.g. serotonin acting on presynaptic 5-HT_{2A} receptors can inhibit DA release.

Inverse agonist: has opposite effect on receptor to the pure agonist, e.g. beta-carbolines in the case of the BZD receptor.

Kinetics: the relationship between the dose of a drug and its serum levels. Zero-order kinetics is the exponential relationship between the dose of a drug and its serum levels, e.g. in the case of phenytoin: because enzymes responsible for its destruction and excretion are saturated at levels required for its therapeutic effects.

Ligand: compound that specifically binds to a receptor.

Narcotic: redundant term first describing sleep-inducing drugs and later meaning morphine-like analgesics.

Non-substrate inhibitors: analogues that bind to the substrate site on a transporter but are not translocated into the cell, e.g. β -threo-benzoyloxy-aspartate in the case of excitatory amino acid transporters I and II.

Nooceptive (nootropic): drugs that improve cognitive and memory functioning.

Opiate: drugs from juice of the poppy *Papaver somniferum*. During opiate withdrawal noradrenergic neurones are activated with increased release of NA. Opiates are found in compounds like Solpadeine (paracetamol, codeine phosphate, caffeine) and Solpadol (paracetamol, codeine phosphate), which renders the liable to being abused. Codeine is converted to morphine in the body and co-administration of paroxetine may prevent this conversion with resultant reduction in analgesia.

Opioid: any substance with morphine-like actions; use is often confined to synthetic narcotics not derived from *Papaver somniferum*. Opioids can be divided into μ (Mu) opioid agonists such as morphine and methadone, and mixed agonist-antagonists like pentazocine. The latter can induce withdrawals in people taking the former. Also, pentazocine can cause a psychotic state, including hallucinations. Levomethadyl acetate (LAAM) is a long-acting opioid agonist. Buprenorphine is a partial agonist at μ opioid receptors.

P450 (CYP) enzymes: These cytochrome enzymes⁶⁷⁹ are a loose group of mixed-function oxidases found mainly in the liver, but also in bowel and brain. The 450 refers to the 450 nm wavelength of the red pigment in the enzyme-containing vesicles. Classification (families and subfamilies) is based on amino acid sequence and this determines affinity for substrates (e.g. for CYP2D6: CYP = P450; 2 = family; D = subfamily; 6 = specific gene). The following enzymes are of most relevance to psychiatry⁶⁸⁰:

⁶⁷⁸ P450 enzymes became very important after erythromycin inhibited enzymatic breakdown of the antihistamine astemizole, accumulation of the latter leading to arrhythmias.

⁶⁷⁹ Also called microsomal enzymes after tiny vesicles of endoplasmic reticulum origin that contain the enzymes.

⁶⁸⁰ Only examples of inhibitors and substrates given here – for updates see relevant websites, e.g. www.drug-interactions.com. Therapeutic and toxic effects are a result of free (not bound) drug levels. Adverse effects may therefore arise despite having drug levels in the 'therapeutic range'. Drug-drug interactions may lead to side effects and may or may not increase total serum levels (TSL)

- **CYP1A2** (inhibitors such as cimetidine, fluvoxamine, ketoconazole, grapefruit juice; inducers such as cigarette smoking, omeprazole; substrates such as amitriptyline, olanzapine, methadone, propranolol)
- **CYP2C9/10** (inhibitors such as cimetidine, fluoxetine, fluvoxamine, modafinil; inducers like rifampin; substrates such as phenytoin, warfarin)
- **CYP2C19** (inhibitors such as fluoxetine, fluvoxamine; substrates such as barbiturates, diazepam, divalproex)
- **CYP2D6** (inhibitors such as bupropion, cimetidine, fluoxetine, paroxetine, sertraline, ritonavir, phenothiazine drugs, quinidine; substrates such as codeine, donepezil, lipophilic beta-blockers, TCAs, type IC antiarrhythmic agents, trazodone, venlafaxine, most antipsychotic drugs; inducers like dexamethasone)
- **CYP3A3/4/5** (inhibitors such as diltiazem, fluvoxamine, grapefruit juice, ketoconazole, macrolides, protease inhibitor drugs, verapamil; inducers such as carbamazepine, modafinil, phenobarbital, phenytoin, ritonavir, St John's Wort; substrates such as alprazolam, anovulant pill, buspirone, calcium channel blocking drugs, donepezil, ethosuximide, lamotrigine, midazolam, paracetamol, protease inhibitor drugs, quinidine, statins, steroid drugs, tamoxifen, triazolam)

Together, P4502D6 and 3A4 account for 90% of clinical drug biotransformation. (Leonard, 2003, p. 469) Different races vary in the efficiency with which these enzymes metabolise drugs. For example, risperidone is metabolised by CYP2D6 and 5-10% of Caucasians and 2% of African Americans are slow metabolizers of risperidone. A number of mutations (genetic polymorphism due to alterations in genetic sequence) of the gene for CYP2D6 have been discovered. Such variations in enzymes may lead to inactive forms or failure to activate prodrugs (e.g. codeine conversion to morphine by CYP2D6).

According to a 'preliminary report on a pilot study', moving from Asia to Europe may slow the rate of metabolism of CYP1A2 substrates like clomipramine because of dietary changes. (Allen ea, 1977)

Partial agonist: defined either as (a) a drug that acts as an agonist at low concentrations but as an antagonist at higher concentrations, or (b) a drug whose intrinsic activity is somewhere between a full agonist and an antagonist; a partial agonist reduces the effect of a full agonist, although the former has the same qualitative action as the full agonist.

Pharmacodynamics: the mechanism of action of drugs, or what drugs do to the body, e.g. blocking receptors.

Pharmacogenetics: Also called pharmacogenomics, this discipline examines the influence of genetic variation on the success or failure of a drug treatment. The hope is to predict all drug effects. (Collier, 2002; Shurin & Nabel, 2008) For example, clozapine affects many receptors and differences (polymorphisms) in several of the genes encoding these receptors may exert effects on response to clozapine. (Arranz ea, 2000) However, failure to correct for multiple testing and failure of others to replicate these findings leaves such interesting potential leads without support. Some workers failed to find any association between serotonin receptor genes and treatment response. (e.g. Tsai ea, 2000) Barnes ea (2003, p. 496) suggested that 'the receptor affinities of [atypical antipsychotics] appear to concur closer to side-effects than response profile'. Sensitivity to side-effects of paroxetine seems to correlate with a variant of the 5-HT_{2A} receptor, i.e. HTR2A C/C genotype. (Murphy ea, 2003a) Response to mirtazapine among depressed elderly may be predicted by the APOE4 allele. (Murphy ea, 2003b) Patients in Taiwan with the short-form polymorphism of the MAO-A gene promoter had a greater response to mirtazapine than did those with long-form polymorphism. (Tzeng ea, 2009) A mutation involving CYP2D6 may be associated with adverse reactions to tricyclic antidepressants; a similar relationship exists between HLA-B*1502 and carbamazepine. (Ingelman-Sundberg, 2008) A meta-analysis conducted by Kato and Serretti (2008) found that TPH1 218C/C genotype was associated with improved antidepressant response as was the Met variant within the BDNF 66Val/Met polymorphism; a trend toward better antidepressant response in Asians was associated with variable number of tandem repeats polymorphism within intron 2 (STin2) 12/12 genotype; and 5-HTTLPR I and HTR2A-1438G/G modulated risk of side-effects of antidepressants, especially when SSRIs were employed. Other work (Licinio ea, 2009) suggests that the rs61888800 SNP region of the BDNF gene may be associated with antidepressant response in major depression. A region (rs10795189) on

of a drug. One drug may displace another, protein-bound drug. Most free drug levels represent 10% or less of TSL in serum, so that large displacement of bound drug may only slightly alter TSL. Lithium toxicity may follow addition of an NSAID or a thiazide diuretic.

chromosome 10p15 may influence the prophylactic action of lithium in bipolar disorder. (Perlis et al., 2009) Ising et al. (2009), in a genomewide association study, found that multiple genetic factors combined with clinical features in predicting antidepressant drug treatment response. Another genomewide association study (Uher et al., 2010) found single-nucleotide polymorphisms in two intergenic regions containing copy number variants on chromosomes 1 and 10 that seem to be important in clinical response to escitalopram and nortriptyline.

The allele sequence associated with normal (i.e. 'extensive') enzyme function is coded by the wild-type gene and this is given the suffix '*1'. Following this, different genetic sequence polymorphisms are numbered in sequence: *2, *3. Multiple copies of a functional CYP enzyme can be found that leads to excess enzyme activity or there may be inactivating polymorphisms that decrease or nullify enzyme activity.

Drug metabolism CYP phenotypes are rather confusingly classified as:

Poor – absent active enzyme gene allele (AEGA); reduced metabolism is associated with increased medication levels and more side-effects at standard doses

Intermediate – 1 active and 1 inactive allele or 2 alleles with diminished activity

Extensive (normal) – possess the normal 2 copies of fully AEGAs for a given microsomal enzyme; associated with predictable response to usual doses of medication

Ultrarapid - multiple copies of AEGAs; increased metabolism leads to sub-therapeutic serum levels of medication

Variation between ethnic groups in allele frequencies is important, e.g. 4-10% and 1-3% of Caucasians and Black Americans and Chinese have no CYP2D6 enzyme. The tiny number of patients that lack AEGAs for both CYP2D6 and CYP2C19 will experience side-effects with most antidepressants and should probably be tried on drugs that are not substrates for CYP2D6 or CYP2C19 (e.g. mirtazapine and bupropion). (de Leon et al., 2006)

'Theranostics' (therapeutics-[diag-]nostics) refers to the development of ways of matching people to optimal drug treatments; immunoassay techniques have been developed to predict which hepatitis C virus genotype are more or less resistant to treatment; its application to psychiatry is in its infancy.

Pharmacokinetics: the drugs passage through the body, i.e. what the body does to a drug: absorption, distribution⁶⁸¹, metabolism, excretion. (Ashton & Harrison, 1994) Fractional absorption (the completeness of absorption) is measured as the 'area under the curve' or AUC when concentration in plasma is plotted against time. Oral drugs are mainly absorbed through the wall of stomach and small intestine. Absorption depends on drug ionization state which is in turn is dependent on pH. Psychotropics are highly ionized due to gastric acidity and so their movement across lipid cell membranes is blocked; they are therefore mostly absorbed via the small intestine. Some drugs are excreted with bile and reabsorbed in the distal small intestine (entero-hepatic circulation). Anticholinergic drugs may delay absorption of other drugs with the result that co-administered medication reaches higher concentrations in plasma. This matters little when drugs are administered over a prolonged period since a drug's steady state⁶⁸² is mainly dependent on metabolism (rather than absorption). *Clearance* (CL) is the rate of drug elimination (in litres/hour) = product of K_e (elimination rate constant) and volume of distribution (V_d , see elsewhere in text), i.e. $CL = K_e V_d$; if clearance remains constant the rate at which the body removes a drug is a function of the concentration of the drug.

Protein binding: The percentage of a drug bound to plasma proteins. Competition for binding sites are particularly important when the patient is taking warfarin or digoxin. The majority of psychotropic drugs are basic and bind mainly to albumin⁶⁸³. Most psychotropic drugs are highly protein bound and can displace warfarin⁶⁸⁴ or digoxin with potential complications.

⁶⁸¹ **Distribution of a drug**: When a drug reaches the systemic circulation it equilibrates between the blood compartment and the tissues, i.e. it distributes. Factors affecting distribution include the percentage of drug bound to plasma proteins and the tissues, solubility in lipid and water, size of the molecule, and pH partition. See *apparent volume of distribution* in main text. The use of the word 'apparent' here is because some drugs may have huge distribution values (e.g. hundreds of litres!).

⁶⁸² **Steady state**: when a drug is given a number of times (multiple dosing) the absorbed drug is added to that already in the system and plasma levels rise until a steady state occurs, i.e. when the availability of the drug is the same as the removal rate of the drug. This usually occurs after 4 to 5 drug half-lives. Apart from obvious allergy or overdose, the practitioner is generally in a position to consider tolerability (and to a lesser extent efficacy) when steady state is reached.

⁶⁸³ Acid drugs bind to $\alpha 1$ -glycoprotein.

⁶⁸⁴ In a patient on warfarin, check the INR a few days after starting/stopping other drugs.

Psychodysleptic: any drug producing abnormal mental phenomena, especially cognitive and perceptual.
Regulation of receptors: the number of receptors, which are constantly being degraded, results from a balance between transcription of receptor RNA, leading to increased numbers, and receptor degradation. Receptors can be pulled inside the cell, as with G-protein-coupled receptors, following activation by NT, leading to down regulated by virtue of less receptor being available for further stimulation. Depending on the receptor, phosphorylation of certain amino acid residues by a kinase may increase or decrease receptor function. (Hamblin, 1997)

Steady-state equilibrium (steady-state): where amount of drug eliminated between doses equals the dose itself – reached after about 4-5 half-lives; the serum level reaches a steady plateau. This is discussed further in a footnote. When taking samples for plasma levels one should note how long it was since the last dose since apparent non-compliance (e.g. no drug detected) may be because of differing sampling times.

Tachyphylaxis: (a) rapid onset of tolerance to a drug, e.g. tolerance to sedation with BZDs can occur even as their plasma levels are rising; (b) loss of drug efficacy during long-term treatment; and (c) loss of drug efficacy after repeated drug exposures over time (e.g. Amsterdam et al [2009] found evidence for the third possibility with antidepressants in adults with bipolar II disorder with major depression).

Tricyclic: contains 3 rings in its structure. Examples are TCAs, cyproheptadine (Periactin, an appetite stimulant), and carbamazepine (anticonvulsant, mood stabiliser, and treatment for neuralgia).

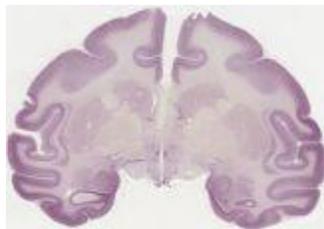
Up-regulation: ‘hypersensitivity’ of receptors; often follows prolonged receptor blockade; possibly involves increased receptor synthesis.

V_{max}: maximum transport rate across membranes, as with 5-HT.

Volume of distribution: ratio between amount of drug in body and plasma concentration. *Apparent volume of distribution* or V_d = extent to which the drug equilibrates outside the blood compartment: small and large volumes indicate that the drug is mainly retained within the blood compartment or that a significant part is in the tissues respectively. Most psychoactive agents are very soluble in lipid and big volumes of distribution. Of course, lipid solubility is needed if the drug is to pass the blood-brain barrier. In this regard, it is important to note that there are no openings (fenestrations) between the endothelial cells of capillaries in the brain. A drug must therefore pass through the cell in order to access the brain.

Acetylcholine (Ach)

Acetylcholine is a quaternary amine. Acetyl coenzyme A (derived from glucose in neuronal mitochondria) plus choline (from the liver) in the presence of choline acetyltransferase (CAT) form Ach and a coenzyme. Giving choline because the enzyme is not fully saturated increases Ach synthesis. Ach can be hydrolysed by acetylcholinesterase or released into the synapse to act on its receptors. There are 2 main types of Ach receptor, nicotinic and muscarinic. Most of the brain’s cholinergic receptors are muscarinic, and there are at least 5 subtypes, M1-M5. They are linked to G-proteins and a variety of second messengers.⁶⁸⁵ The cholinergic nicotinic receptor⁶⁸⁶ is a ligand-gated ion channel composed of 5 subunits which are encoded by different genes. The $\alpha 7$ -nicotinic receptor gene may be involved in the auditory sensory gating defect reported in schizophrenics. (Freedman et al, 1997)



Nucleus basalis of Meynert

⁶⁸⁵ Muscarinic receptors display the structural characteristics of 7 transmembrane proteins. M1 to M3 stimulate the hydrolysis of phosphoinositol and lead to increased intracellular calcium together with cAMP. M4 to M5 inhibit adenylyl cyclase. M1 receptors have a high affinity for the anti-muscarinic agent pirenzepine, while M2 receptors have a low affinity for this agent.

⁶⁸⁶ α [$\alpha 2$ -9] and β [$\beta 2$ -4] families.

In Alzheimer's disease, the cholinergic cell bodies in the basal forebrain nuclei (nucleus basalis of Meynert⁶⁸⁷ or nucleus gigantocellularis, septum, nuclei of diagonal band), that innervate the whole cortex, degenerate, a fact that is reflected in loss of cortical CAT and Ach. The balance between Ach and other transmitters in the striatum, such as dopamine, appears to be critical in both Parkinson's and Huntington's diseases in which anticholinergic drugs respectively improve and worsen the movement disorder. (Albin et al, 1989) CAT activity is unaffected in both Pick's disease and dementia of the frontal lobe type. (Procter, 1997)

The cholinergic system, which is very important for memory functions, originates in Meynert's nucleus (see above), the diagonal band of Broca, and the septal nucleus⁶⁸⁸. Meynert's nucleus projects throughout the cortex and to the hippocampus and amygdala, whereas the latter two centres project to the cingulate gyrus and the hippocampus. A third group of neurones provides local circuits to the basal ganglia.

There are 2 types of cholinesterase: acetylcholinesterase⁶⁸⁹ and pseudo-, butyl- or non-specific cholinesterase⁶⁹⁰. Outside the nervous system the 2 types are distributed differently.

Physostigmine⁶⁹¹, neostigmine and edrophonium inhibit acetylcholinesterase. Physostigmine, normally given intravenously for TCA (anticholinergic) poisoning has a very short duration of action, although an oral sustained-release preparation is being tested clinically. Physostigmine can cause nausea and vomiting. Another agent which has become available is galantamine (Reminyl), a component of snowdrops and daffodils, which is both a cholinesterase inhibitor and nicotine agonist, the latter action leading to Ach release.

Donepezil reversibly inhibits acetylcholinesterase but not pseudocholinesterase. Tacrine (Cognex), which is hepatotoxic, reversibly inhibits both types of cholinesterase; it also inhibits CYP450 1A2 and therefore tacrine levels are increased by co-administered cimetidine. Rivastigmine (Exelon) inhibits acetylcholinesterase only, but itself reverses this action over some hours, so-called pseudoreversibility.

Metrifonate, an antischistosomal agent, does not inhibit cholinesterase until metabolised to the organophosphate 2,2-dichlorovinyl dimethyl phosphate (DDVP), an irreversible inhibitor of both species of cholinesterase that has been associated with muscle weakness.

Botulinum toxin inhibits, and Black Widow spider venom facilitates, the release of Ach from the presynaptic neurone. Ach acts on nicotinic and muscarinic receptors. Nicotine acts agonistically, and d-tubocurarine, succinylcholine, decamethonium, hexamethonium, fuxamethonium and gallamine act antagonistically at cholinergic nicotinic receptors, while muscarinic receptors have their own agonists⁶⁹² and antagonists⁶⁹³. Muscarine and nicotine are mushroom and tobacco alkaloids respectively. Drugs like succinylcholine and decamethonium do not compete with Ach for the receptor site, instead causing prolonged depolarisation of the receptor rendering it insensitive to Ach. Low dose Ach is excitatory at nicotinic receptors in low doses, whereas in high doses it causes blockade by depolarisation; it is inhibitory at muscarinic receptors. Similarly, low doses of nicotine produce stimulation in the periphery, whilst high doses block nicotinic receptors with paralysis of the neuromuscular junction.

The effects of Ach on the peripheral autonomic system are muscarinic, whilst those on autonomic ganglia and the neuromuscular junction are nicotinic.

Cholinergic drugs or poisons, such as physostigmine and organophosphate fertilisers, can acutely cause a depressed, listless, fatigued, irritable state, with later seizures, myoclonus, and delirium.

Anticholinesterases such as physostigmine inhibit acetylcholinesterase, with accumulation of Ach at cholinergic synapses. Physostigmine does not reverse the cardiotoxic effects of TCAs but intravenous physostigmine may reverse transient psychosis secondary to antimuscarinic drugs.

Benztropine⁶⁹⁴, and to a lesser extent benzhexol⁶⁹⁵ and orphenadrine⁶⁹⁶, inhibit DA uptake as well as blocking cholinergic receptors.

⁶⁸⁷ Degeneration of the nucleus basalis of Meynert, a major source of cholinergic innervation (and efferents to the suprachiasmatic nucleus), could underlie sleep problems in dementia. (Klaffke & Staedt, 2006)

⁶⁸⁸ The **cholinergic basal forebrain** consists of the nucleus basalis of Meynert, the diagonal band of Broca, and the medial septum.

⁶⁸⁹ Mainly found in neurones in the brain and is the main enzyme for destroying Ach at cholinergic synapses.

⁶⁹⁰ Found mainly in glial cells in the brain, and it destroys Ach that diffuses to these cells.

⁶⁹¹ Physostigmine is found in Calabar bean (*Physostigma venenosum*).

⁶⁹² Muscarine, carbachol, pilocarpine, methacholine.

⁶⁹³ Atropine, benztropine, procyclidine, hyoscine.

⁶⁹⁴ Not available from 2003.

⁶⁹⁵ Unavailable from 2002.

It has been suggested that, unlike atypical antipsychotics, typical antipsychotics do not release Ach in the medial prefrontal cortex and that this may account for adverse cognitive side-effects. (Meltzer, 2003)

*Catecholamines*⁶⁹⁷

Most noradrenergic cell bodies, which innervate the complete cortex, are found in the locus coeruleus, a dorsal pontine nucleus beside the fourth ventricle. Yohimbine, central α -2 adrenergic antagonist, increases locus coeruleus firing and hence noradrenaline release, causing anxiety in humans; the α -2 agonist clonidine reduces locus coeruleus firing, and has a modest anxiolytic effect.

Synthesis of catecholamines involves conversion of phenylalanine to tyrosine, which is converted to DOPA and this is changed to dopamine (DA); the latter can be converted to noradrenaline (NA; norepinephrine), from which adrenaline (epinephrine) is derived. NA can be broken down to (a) normetanephrine and then to 3, hydroxy 4 methoxy mandelic acid, or (b) 3,4-dihydroxy mandelic acid, or 3,4-dihydroxy phenyl glycol, the latter being degraded in turn to 3-hydroxy 4 methoxy phenyl glycol. The rate-limiting step in catecholamine synthesis is the conversion of tyrosine to DOPA by tyrosine hydroxylase. NA synthesis is blocked by α -methyl-para-tyrosine (AMPT) which inhibits tyrosine hydroxylase.

DA, in contrast to l-DOPA (levodopa), does not cross the blood-brain barrier. Clinically, l-DOPA is given with a peripherally acting inhibitor of DOPA decarboxylase such as carbidopa (in Sinemet) or benserazide (in Madopar). This ensures efficient delivery of l-DOPA into the CNS⁶⁹⁸. Once in the CNS, l-DOPA is converted to DA by l-amino acid decarboxylase.

All DA receptors, currently D1-5, are linked to G proteins. All 5 receptor subtypes are found postsynaptically, while D2 and D3 are also found presynaptically. D2 exists as two isoforms: D_{2short} and D_{2long}. D1 (dopamine 1) is linked to cyclic AMP (cAMP) and D2 is not linked to cAMP. The details of the distribution of their mRNAs can be summarised thus: D1 (caudate, putamen, olfactory tubercles, nucleus accumbens, amygdala, cortex), D2 (mainly basal ganglia), D3 (mainly limbic), D4 (mainly cortical fields), and D5 (parafascicular nucleus of thalamus, hippocampus, dentate nucleus, many cortical fields). (Mansour ea, 1998) D2 blockade seems to be responsible for antipsychotic effects. D2 antagonism from the strongest to the weakest can be illustrated as follows: haloperidol > risperidone > perphenazine > chlorpromazine > clozapine. Risperidone is strongly antagonistic at D2 receptors, antagonistic at 5-HT₂ receptors, and, in nanomolar doses, it has affinity for α -2 receptors. The benzamides sulpiride and remoxipride are specific D2 antagonists, while another benzamide, amisulpride (Solian) is highly selective for D2 and D3 receptors. The dibenzothiazepine quetiapine (Seroquel) has a greater affinity for 5-HT₂ receptors than for D2 receptors.

Remoxipride, in fact, has high selectivity and low affinity for D2 receptors. Ziprasidone acts on D1, D2, and D3, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1D} receptors. However, its development was slowed by cardiac suppression (prolonged QT interval) with the risk of tachyarrhythmias. (Baldessarini, 1999)

Clozapine has low D2 affinity, equal affinity for D1 and D2, and high D4 affinity; low D2 and high D4 affinities may relate to enhanced efficacy in schizophrenia. It also blocks 5-HT₂ receptors and has high affinity for 5-HT₆ and 5-HT₇. Clozapine has relatively strong affinities for α -1 (postsynaptic) and α -2 receptors. Clozapine's affinity for D4 receptors is not unique among antipsychotic drugs. D3 receptors are expressed in the limbic system and have a possible role in schizophrenia. D3, D4, and D5 receptors are found in limbic and frontal areas. D3 and D4 receptors are subtypes of D2, and D5, which is found in the hippocampus, is a subtype of D1. DA is degraded to dihydroxy phenyl acetic acid and thence to homovanillic acid (HVA). During pregnancy oestrogen levels are raised, and they may have an antipsychotic action via DA receptors, with up-regulation of receptor numbers. After delivery, the fall in oestrogen levels leaves the receptors exposed.

Antipsychotic drugs acutely increase the dopaminergic neuronal firing rate, only later increasing DA metabolite levels. Very low doses appear to block autoreceptors selectively, leading to increased DA concentrations in the absence of postsynaptic blockade. (Wilcox ea, 1998)

⁶⁹⁶ Withdrawn, 1999.

⁶⁹⁷ In 1921, Cannon and Uridil used the name 'sympathin' for the substance released when sympathetic nerves were stimulated; this was later identified as noradrenaline by von Euler and shown to be present in brain by Holtz. Dopamine was discovered as a brain neurotransmitter by Arvid Carlsson in the late 1950s. Carlsson (Nobel Prize, 2000) suggested dopamine blockade as the mechanism of action of antipsychotic drugs.

⁶⁹⁸ It prevents levodopa metabolism in the GIT, diminishes GIT upset, and gives higher blood levels with smaller doses.

Chronic blockade of nigrostriatal D2 receptors by drugs may lead to upregulation of these receptors (increased sensitivity and/or numbers) in an attempt to overcome the blockade⁶⁹⁹. This is the 'dopamine supersensitivity' theory of tardive dyskinesia. The same theory has been used to explain schizophrenia itself.(McKenna, 2007, p. 149) A different theory for tardive dyskinesia implicates GABA deficiency, and is based on such findings as low CSF GABA levels in dyskinetic cases of schizophrenia.(Thaker ea, 1987) D2 occupancy can be measured using ¹¹C-raclopride as a ligand for PET and ¹²³I-iodobenzamide as ligand for SPECT. Typical antipsychotic drugs such as haloperidol bind tightly to D2 receptors and dissociate slowly, whereas clozapine (and quetiapine) binds loosely and dissociates rapidly; clozapine's occupancy of D2 receptors is transient. At doses of 5-20 mgs/day, olanzapine shows greater 5-HT₂ than D2 blockade, but at bigger doses 5-HT₂ occupancy approaches saturation and D2 occupancy still increases. The latter phenomenon parallels the increased likelihood of experiencing extrapyramidal side effects (EPS). Similar dose-related events have been demonstrated for risperidone. However, unlike clozapine and quetiapine, risperidone binds tightly to D2 receptors.(Kapur & Seeman, 2000)

Noradrenergic receptors are divided into α (alpha)⁷⁰⁰ and beta (β) subtypes. Alpha-1 and beta receptors are chiefly postsynaptic. Alpha-2 receptors are both pre- and post-synaptic. Beta (β) receptors are divided into β_1 , 2, and 3. All are linked to adenylate cyclase but sensitive to different antagonists. Beta-1 receptors are found in the heart where they are targeted by beta-blockers. Beta-2 receptors are found in lung⁷⁰¹, uterus and voluntary muscle. Beta-3 receptors are chiefly associated with adipose tissue where they are involved in energy metabolism and thermogenesis from fat, especially in response to NA. Sibutramine increases NA peripherally at beta-3 receptors, causing weight loss by heat production and increased consumption of oxygen.

NA is released by amphetamine, and phenylephrine acts as a noradrenergic receptor agonist. Clonidine, which has been known to cause depression, is a alpha-2-agonist, isoprenaline is a beta-agonist, and phentolamine and phenoxybenzamine are alpha-antagonists. Clonidine reduces anxiety levels by blocking presynaptic alpha-2-receptors, thereby producing downregulation. Beta-antagonists include propranolol, pindolol, and acebutalol.

Amitriptyline inhibits NA reuptake into the presynaptic neurone, whereas the MAOIs, phenelzine and tranylcypromine, inhibit degradation of NA by monoamine oxidase (MAO⁷⁰²). Venlafaxine (Efexor) is a serotonin and noradrenaline reuptake inhibitor or SNRI. Catecholamine reuptake inhibition may require higher doses of venlafaxine than those needed for 5-HT reuptake inhibition. Milnacipran (Ixel), a cyclopropane derivative, is another SNRI, although it is more potent for NA than for 5-HT. Duloxetine is a dual uptake inhibitor that is claimed to block NTs at starting and therapeutic doses. Amphetamine and amantidine facilitate DA release. Apomorphine act as an agonist at DA receptors, while the antipsychotic drugs haloperidol and chlorpromazine are classical examples of DA receptor antagonists. Nomifensine inhibits DA reuptake, and the MAOI (actually MAO-B inhibitor at low doses, e.g. 10 mg/day) L-deprenyl (selegiline) inhibits dopamine degradation by MAO. L-deprenyl, which is metabolised to methamphetamine and amphetamine, has antidepressant activity in high dosage (c 30 mg/day) and it may require the same dietary restrictions as classic MAOIs at such doses.

Bromocriptine (Parlodel) is an ergot alkaloid and mixed DA agonist-antagonist. At low doses it is an agonist at presynaptic D2 receptors, reducing DA release. At higher doses it has a direct agonist action on postsynaptic DA receptors. Its main uses are for Parkinson's disease, for antipsychotic-induced hyperprolactinaemia and galactorrhoea, and in neuroleptic malignant syndrome. Other claimed applications include alcohol or cocaine withdrawal amelioration, depression, drug-induced Parkinsonism, tardive dyskinesia, and anxiety disorders, including OCD. Side effects include nausea, headache, dizziness, vomiting, abdominal cramps, constipation, syncope, cardiac arrhythmias, worsening of angina, and, rarely, psychosis. Caution is necessary in the presence of hypertension and hepatic or cardiovascular disease. It should be avoided in pregnant or nursing mothers, and the contraceptive pill may interfere with its activity. The D2 agonist cabergoline (Cabaser, Dostinex) is related to bromocriptine.

⁶⁹⁹ By analogy with denervation sensitivity when ACh motor end plate receptors multiply following neuro-muscular disruption.

⁷⁰⁰ 1a-c and 2a-c.

⁷⁰¹ Target of bronchodilators.

⁷⁰² E. A. Zeller (1907-87) of Basel separated MAO from diamine oxidase in 1938; in 1952, in the US, he discovered that iproniazid inhibited MAO. MAO is found on the outer mitochondrial membrane.

Dopamine prevents prolactin secretion by pituitary lactotrophs. (McCollam & O'Shea, 2004) TRH, as well as causing TSH secretion, stimulates prolactin release: with reduced T4 one sees increased prolactin because of increased TRH. Drugs inhibiting DA secretion (methyl dopa, reserpine, opiates, H2-receptor blockers) or inhibit DA action (neuroleptics, metoclopramide [a benzamide used as an antiemetic]) can cause hyperprolactinaemia. Oestrogens, including the contraceptive pill, cause lactotroph excess, and hence hyperprolactinaemia. Possession of the DRD2AI allele may lead to higher prolactin levels in patients exposed to antipsychotic drugs. (Young et al, 2004) The end result of hyperprolactinaemia is gynaecomastia in males and galactorrhoea and amenorrhoea in females. Pharmacological causes of gynaecomastia include alcohol, cannabis, cyproterone acetate, digitalis, oestrogen ingestion, and spironolactone.

After arising in cell bodies in the brainstem locus coeruleus, noradrenergic fibres project diffusely throughout the whole brain, including cortex, limbic lobe, brainstem, cerebellum and cord.

Dopaminergic cell bodies of the brainstem substantia nigra⁷⁰³ project to the caudate nucleus to synapse with cholinergic neurones that project to the putamen. Thence, GABAergic neurones descend to synapse with the dopaminergic cell bodies in substantia nigra. In other words, nigrostriatal DA axons connect with cholinergic caudate interneurons, and a striato-nigral feedback loop is set up that also involves GABAergic neurones.

There are, in fact, 4 main dopaminergic pathways in the brain. The *nigrostriatal pathway*, mentioned above, is part of the extrapyramidal system, and is therefore involved in movement control; as already stated, fibres project from the **substantia nigra** to the basal ganglia⁷⁰⁴ (corpus striatum – production of smooth/coordinated movement). The *mesolimbic pathway* arises in the ventral tegmental area (**VTA**) of the midbrain and projects fibres to limbic areas such as the nucleus accumbens (Cocaine blocks DA reuptake into presynaptic dopaminergic terminals, greatly elevating extracellular DA levels in the nucleus accumbens⁷⁰⁵, thereby activating the physiological 'reward system'). This pathway appears to be important for the experience of pleasure, the euphoric effects of drugs, and probably also for the positive symptoms of psychoses, such as delusions and hallucinations. The *mesocortical pathway*, also arising in the **VTA** but projecting mainly to limbic cortex, may play a role in the generation of the negative and cognitive symptoms of schizophrenia. One theory is that such clinical deficits are due to a primary DA deficiency in the prefrontal cortex (PFC). However, other possibilities are neuroleptic-induced D2 blockade and blockade of 5-HT_{2A} receptors by excess 5-HT (stimulation of rat brain 5-HT_{2A} receptors increase synthesis and release of DA and antagonists at this receptor decrease the stimulant effects of amphetamine; phencyclidine-induced decrease in the activity of rat frontal cortical dopaminergic terminals is reversed by antagonists at the 5-HT₂ receptor). Finally, the *tuberoinfundibular pathway* projects from the **arcuate nucleus** of the hypothalamus to the anterior pituitary, and controls prolactin release⁷⁰⁶.

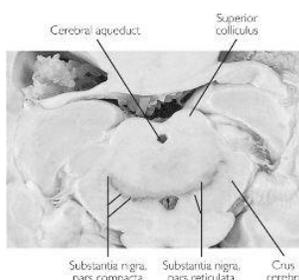
In Alzheimer's disease, the cells of the locus coeruleus degenerate, with a reduction in concentrations of dopamine-β-hydroxylase. The restricted distribution of DA in the brain compared to other transmitter systems may explain why transmitter treatment has been more successful in Parkinson's disease than in other disorders. (Perry, 1991)

⁷⁰³ **Neuromelanin**, a product of catecholamine oxidation, is the dark pigment present in pigment bearing neurons of four deep brain nuclei: the substantia nigra pars compacta part, the locus coeruleus ("blue spot"), the dorsal motor nucleus of the vagus nerve, and the median raphe nucleus in the pons. In the human these nuclei are not pigmented at birth but become so during maturation.

⁷⁰⁴ Disease of the basal ganglia affects self-initiated actions more than actions cued by the environment.

⁷⁰⁵ 'Nucleus that lies beside'; the ventral striatum. (See e.g. Fladung et al [2010] in relation to anorexia nervosa.) The nucleus accumbens lies below the ventral border of the internal capsule and merges with the caudate nucleus and putamen in humans.

⁷⁰⁶ The infundibulum, or median eminence, gives rise to the pituitary stalk at the base of the hypothalamus, i.e. in the floor of the third ventricle.



Substantia nigra

Many drugs and toxins are capable of causing *Parkinsonism*, e.g. alcohol withdrawal, alpha-methyl dopa, antipsychotic drugs, reserpine, carbon monoxide, cyanide, cytosine arabinoside, diazepam (in big doses), lithium, manganese, MAOIs, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine⁷⁰⁷, metoclopramide, organophosphates, reserpine, SSRIs, kava, captopril, cinnarizine, flunarizine, sodium valproate, phenytoin, and tetrabenazine. The list of disorders causing Parkinsonism is also lengthy, e.g. vascular disorders, degenerative disorders (e.g. progressive supranuclear palsy), infections (e.g. neurosyphilis), metabolic conditions (e.g. hypothyroidism), and other disorders (e.g. cerebral tumours and subdural haematoma). *5-hydroxytryptamine (5-HT; serotonin)*⁷⁰⁸

5-HT, an indoleamine⁷⁰⁹ and phylogenetically the oldest of the neurotransmitters, is synthesised in the raphe nuclei. Tryptophan may be converted to indoleacetate via tryptamine and indoleacetaldehyde, or through 5-hydroxytryptophan to 5-HT⁷¹⁰, an indoleamine, and then to 5-hydroxy-indole acetaldehyde and 5-hydroxy-indoleacetate. The availability of tryptophan is probably the rate limiting function in 5-HT synthesis, rather than the enzyme tryptophan hydroxylase, which converts tryptophan to 5-hydroxytryptophan, although not all authors agree. (Mansour ea, 1998) Tryptophan hydroxylase is inhibited by para-chlorophenylalanine. L-tryptophan induces the hepatic enzyme tryptophan pyrrolase. The latter can be occupied by adding nicotinamide 1 gram daily.

There are an increasing number of classes of 5-HT receptor, especially 5-HT1-7, 5-HT1 being further subdivided into 5-HT1A-D. However, the number of 5-HT receptors is expanding rapidly (at least 15 in 2007) and all such statements rapidly become dated. 5-HT1, 1D, 2, 3, 6 and 7 may be particularly relevant in schizophrenia.

5-HT1A receptors include autoreceptors that inhibit serotonergic cell firing, and postsynaptic receptors. Agonists include buspirone, a partial agonist at 5-HT1A receptors pre- and postsynaptically. 5-HT1C receptors are found mainly in the choroid plexus, and affect mood and appetite. To make life more complicated, 5-HT1C is now thought to be the same receptor as 5-HT2 (Musselman ea, 1998) and 5-HT2 receptors are divided into A, B, and C subtypes. LSD activates 5-HT2 receptors whilst a number of 'atypical' antipsychotic drugs inhibit these receptors. 5-HT1D receptors are found on intracranial blood vessels, and cause vasoconstriction. LSD acts on serotonergic receptors. 5-HT is released by d-fenfluramine (causing prolactin release - halogen-containing amphetamine analogues like fenfluramine are more powerful at causing 5-HT release than are those lacking such atoms), reserpine, and tetrabenazine. LSD, mescaline, and methyltryptamine are agonists at dopamine receptors. Methysergide, cinnanserine, cyproheptadine, and metorgolide act as antagonists at that receptor. Clomipramine (chlorimipramine), nortriptyline, and fluoxetine act as serotonin reuptake blockers. MDMA ('ecstasy') blocks 5-HT uptake and induces its release from neurones, and clorgyline and tranylcypromine effect inhibition of 5-HT metabolism by MAOI.

Clomipramine inhibits 5-HT reuptake without inhibiting NA reuptake. However, its metabolite desmethylclomipramine is a strong NA reuptake inhibitor. The first really specific serotonin reuptake

⁷⁰⁷ MPTP, a toxic metabolite formed during synthesis of pethidine.

⁷⁰⁸ Brodie discovered a vasoconstrictor in the serum in 1900; Rapaport named it serotonin in 1948 and identified it as 5-HT; and 'enteramine', found in gut enterochromaffin cells, was shown to be 5-HT by Erspamer. Hamlin and Fisher synthesised 5-HT in 1951. Its presence in the brain was demonstrated by Twarog and Page. Perhaps reflecting its long history in evolutionary terms, 5-HT is involved in many different emotions and behaviours, a fact that may help to explain the broad range of applications for serotonergic antidepressant drugs. (Stein, 2003, p. 58)

⁷⁰⁹ Melatonin is also an indoleamine.

⁷¹⁰ The latter step being catalysed by aromatic amino acid decarboxylase.

inhibitor (SSRI) was zimeldine (Zelmid, now withdrawn from the market because of neurological sequelae).

The most selective SSRI is citalopram, but paroxetine is the most potent SSRI. Therefore, selectivity does not correlate with potency, citalopram being only one-tenth as potent as paroxetine in terms of serotonin transport blockade.

Ritanserin, a selective '5-HT₂ and 5-HT_{1C}' (but see above) antagonist, reduces the severity of negative symptoms in schizophrenia. (Duinkerke ea, 1993) Lithium might augment TCAs by sensitising postsynaptic 5-HT receptors. Tianeptine is an unusual tricyclic antidepressant that **increases** presynaptic 5-HT uptake. (Curzon & Widlöcher, 1992) However, tianeptine performed poorly in comparison to fluoxetine in one French primary care study of elderly depressives. (Guelfi ea, 1999)

The raphe nuclei are found in the region of the midbrain aqueduct and, like the noradrenergic system, they project widely. Areas innervated include all neocortical areas, temporal lobe, midbrain, hypothalamus, brainstem, cerebellum, and cord.

The therapeutic action of antidepressant drugs may ultimately depend on down regulation of postsynaptic adrenergic beta-1 receptors, or possibly of postsynaptic 5-HT₂ receptors as well. (*vide infra*) Nefazodone⁷¹¹, a relative of trazodone, blocks 5-HT₂ receptors and inhibits serotonin reuptake; 5-HT₂ receptors are downregulated with chronic nefazodone dosing. Increased beta and 5-HT₂ receptor density have been reported in the brains of suicides at post-mortem. (Kendell, 1993)

Weight gain due to psychotropic drugs may relate to antihistaminic and 5-HT_{2C} antagonism.

The 5-HT₃ antagonists ondansetron and granisetron are antiemetics, being employed to counter the side effects of cancer chemotherapy, whereas the SSRI sumatriptan (Imgran) is used to treat migraine.

Olanzapine has a relatively high affinity for 5-HT₆ receptors and risperidone for 5-HT₇ receptors. (Roth ea, 1994)

In Alzheimer's disease, the cell bodies of the raphe nuclei degenerate with an accompanying decrease in 5-HT concentration throughout the cortex.

Regulation of serotonergic neurone

Some of the contents of this section will be a repeat of what has been written already. The surface of the cell body and dendrites of the 5-HT neurone have 5-HT_{1A} receptors that are somatodendritic autoreceptors. When serotonin acts here there is shutdown of outflow of 5-HT from the neurone. These neuronal parts also have α -1 receptors. When NA acts here there is increased release of 5-HT from the cell. The axon terminal has 5-HT_{1D} (terminal) autoreceptors that, when stimulated by 5-HT present in the synaptic cleft, blocks further 5-HT release from the cell. If a drug blocked a 5-HT_{1D} terminal autoreceptor it would reduce serotonin release. Also at the axon terminal is the α -2 heteroreceptor. NA from nearby noradrenergic neurones can diffuse to these receptors and turn off 5-HT release. I.e., 5-HT release can be inhibited by 5-HT or NA. It should be noted that α -2 receptors on noradrenergic neurones are called autoreceptors, but those on serotonergic neurones are called heteroreceptors. In summary, all these receptors, with the exception of α -1 receptors, reduce the effects of serotonin neurotransmission. Finally, the postsynaptic neuronal membrane has its own serotonin receptors: 5-HT_{1A}, 2A, 2C, 3, 4, etc.

The noradrenergic neurones of the locus coeruleus send axons to the raphe nuclei (to synapse with dendrites and soma of 5-HT cells) where they promote 5-HT release, and to the cortex (to synapse with axon terminals of 5-HT cells) where they inhibit 5-HT release.

Gamma aminobutyric acid (GABA)⁷¹²

GABA is formed from l-glutamic acid by the rate limiting enzyme glutamate decarboxylase (GAD)⁷¹³. This conversion depends on vitamin B6 as cofactor. GABA, which has no releaser, is, along with glycine, a major inhibitory NT. B6 deficiency can lead to deficiency of GABA and seizures. Also, picrotoxin (*vide infra*), like bicuculline and pentylentetrazol, blocks the GABA chloride channel with resultant seizures.

⁷¹¹ Dutonin – withdrawn 2003. Unlike trazodone, nefazodone does not antagonise alpha-1-adrenoceptors and is non-sedating. Like trazodone, it is metabolised to the anxiogenic 5-HT receptor agonist, m-CPP. It is also metabolised to hydroxynefazodone, which has similar actions to the parent compound. Krystal ea(1993) gave m-CPP to patients with schizophrenia and controls and reported an exacerbation of positive symptoms in the former and no effect in the latter. To them, this suggested a 'pro-psychotic' rather than a psychotogenic effect, perhaps indicating a role for serotonergic mechanisms in schizophrenia.

⁷¹² 55%, 25% and 1% of brain neurones are GABAergic, cholinergic, and noradrenergic respectively.

⁷¹³ The chief initial source of GABA is glucose which is converted in Krebs cycle into alpha-ketoglutarate and then to l-glutamate. GAD is confined to GABA-producing neurones.

Pre-treatment with bicuculline blocks the actions of BZDs.⁷¹⁴ GABA is removed from the synapse into presynaptic nerve terminals and the surrounding glial cells where it is broken down by alpha-oxoglutarate and further (downstream) products enter Krebs cycle.

There are 2 GABA receptors, A and B.⁷¹⁵ Benzodiazepines combine with the BZD receptor site. The latter forms part of the GABA receptor complex. The BZD-BZD receptor site combination increases the sensitivity of the GABA receptor for the inhibitory transmitter GABA. This is achieved by facilitation of GABA-mediated increase in chloride conductance, resulting in neuronal membrane hyperpolarisation and inhibition of action potential propagation. (Hoffman & Warren, 1993) BZDs require the presence of GABA to produce their effects. Barbiturates do not have this requirement because of their direct action on GABA receptors. Barbiturates act closely with the GABA A receptor to increase chloride ion conductance, thereby reducing neuronal membrane excitability. In higher doses, barbiturates block the effects of excitatory NTs and disrupt membrane function outside the synapse. (Nutt, 1993)

GABA receptors are found mainly in the septo-hippocampal part of the limbic system, and also in the spinal cord.

Flumazenil is a BZD receptor antagonist with little inherent pharmacological activity. It blocks the effects of other BZDs and can provoke acute BZD withdrawal. Only available for intravenous use, flumazenil is used to reverse acute BZD toxicity. β -carbolines are inverse agonists of BZD receptors with resultant anxiety and seizures.

Brain BZD receptors in the brain have been classified as either BZ1 (type 1, omega 1) or BZ2 (type 2, omega 2), while omega 3 receptors are abundant peripherally. Zapelon (Sonata), a novel hypnotic, is thought to bind selectively to BZ1 receptors.

Changes in prefrontal cortical neural circuitry involving GABA may be involved in cognitive dysfunction in schizophrenia. Inhibitory interneurons containing parvalbumin⁷¹⁶ may be reduced in number and there may be reduced expression of the GABA synthesising enzyme glutamic acid decarboxylase⁷¹⁷. These findings suggest a functional prefrontal cortical GABA deficit.

As with so many other NTs, the intrinsic cortical transmitters GABA and somatostatin are diminished in Alzheimer's disease.

Gamma-hydroxybutyrate (GHB, sodium oxybate)⁷¹⁸, an anaesthetic⁷¹⁹, anti-narcolepsy agent, abused drug, and catabolic derivative of GABA, causes nausea and vomiting, muscle stiffness, unconsciousness and seizures and is a drug of abuse.⁷²⁰ Its euphoriant and disinhibiting effects resemble those of alcohol. It may act at GABA_B receptors. GHB increases cerebral DA. It is synergistic with alcohol and may depress respiration. Some effects of GHB are reversed by naloxone in animals. (Jones & Volans, 1999) GHB is a schedule three drug under the *Misuse of Drugs Act*.

Glutamate (glutamic acid)

This NT, the main excitatory NT in the brain, is derived from the cortical pyramidal cells and the hippocampus. It is a non-essential amino acid that cannot cross cell membranes, including the blood-brain barrier. Glutamate is formed from glutamine or aspartate within neuronal terminals. Glutamate is mainly taken from the synapse by a sodium-dependent mechanism into astrocytic processes that surround the synapse wherein it is converted into glutamine by glutamine synthetase⁷²¹. Glutamine is then taken up by

⁷¹⁴ Pentylentetrazol, which is also anxiogenic, was used to induce convulsive therapy before the advent of ECT.

⁷¹⁵ 3-aminopropane, sulphonic acid, and muscimol are agonists for GABA; picrotoxin and bicuculline are antagonists; nipecotic acid and 4-methyl-GABA are reuptake inhibitors; and gabaculine, amino-oxyacetate, and acetylenic GABA inhibit GABA breakdown. Baclofen (Lioresal), a synthetic analogue of GABA, is a central muscle relaxant which depresses polysynaptic but not monosynaptic (e.g. knee jerk) reflexes; it can cause nausea, sedation, confusion, impaired alertness, and muscle fatigue; it is a GABA B receptor agonist. The GABA A receptor is baclofen-insensitive.

⁷¹⁶ Parvalbumin, an allergen implicated in seafood allergy, is a calcium binding albumin found in muscle, endocrine and nervous tissue. It is found in GABA-ergic interneurons, e.g. cortical chandelier and basket cells. It is present in a variety of hippocampal cells.

⁷¹⁷ The density of chandelier neurone axon terminals immunoreactive for the GABA membrane transporter (GAT-1) is reduced in most patients with schizophrenia. There are two types of **parvalbumin cell: chandelier** (with axons targeting initial axon segments of neocortical pyramidal cells with limited coverage of its axons) and **wide arbour cells** (targeting cell bodies and proximal part of dendrites with its axons covering a *wide* area). Chandelier cells may regulate the timing of output of a column of pyramidal cells. Wide arbour cells may inhibit pyramidal cells in nearby columns. It is easy to see how loss of such coordinating functions could disrupt higher cognitive functions in someone with schizophrenia.

⁷¹⁸ 'Liquid ecstasy'; liquid, powder and capsule forms.

⁷¹⁹ Since early 1960s.

⁷²⁰ In Britain it is associated with the rave and dance club scene, is sold in sex shops or can be ordered in the post.

⁷²¹ Glutamine synthetase is not present in neurones.

neurones and converted back into glutamate by glutaminase. Glutamate appears to be neurotoxic if present in sufficient quantity, so-called *excitotoxicity*⁷²². Apart from being a NT, glutamate is involved in synaptic remodelling, learning, neuronal maintenance, and brain development. (Fearon et al, 2000) Depending on agonist preference, there are 4 types of glutamate receptors: NMDA⁷²³, AMPA⁷²⁴, kainate⁷²⁵, and the slower acting metabotropic. The first 3 are linked to ion channels⁷²⁶ whilst metabotropic receptors, of which there are a number of subtypes, are G-protein-linked, act through cAMP or phosphoinositide, and seem to be important in memory function via a mechanism called 'long-term potentiation'. Phencyclidine (PCP) blocks NMDA glutamate receptors causing an indirect inhibition of calcium influx.

In fact, **NMDA receptors** have sites for glutamate, glycine (**co-regulatory site** for the amino acids glycine⁷²⁷ or D-serine that has to be occupied in order for glutamate to open the channel), polyamine, zinc (Zn), magnesium (Mg), as well as PCP. The receptor for PCP is called the sigma-PCP receptor and resides in the ion channel of the NMDA receptor complex.

Normally, glutamatergic fibres from the caudate nucleus have an inhibitory effect on DA release by the globus pallidus. In Huntington's disease, with cell loss in the caudate⁷²⁸, there is excess DA release from the globus pallidus, leading to choreiform movements.

cAMP and PI second messenger systems

(a) cAMP (cyclic 3,5-adenosine monophosphate) second messenger system

Neurotransmitter + receptor → activated G protein → activation of adenylate cyclase causing ATP conversion to cAMP → cAMP activates protein kinase A → protein kinase A phosphorylates (i.e. activates) various intracellular proteins such as cAMP-responsive element-binding protein (CREB) → CREB causes DNA transcription – protein synthesis

(b) PI (phosphatidylinositol) second messenger system

PI (in the cell membrane) → PIP₂ (PI biphosphate) → neurotransmitter binds to receptor and activates a G protein → activation of phospholipase C which hydrolyses PIP₂ to produce IP₃ (inositol triphosphate) and DAG (diacylglycerol) → IP₃ releases calcium from stores leading to calcium-dependent activities (e.g. phosphorylation of proteins by calcium-dependent kinases) and DAG activates protein kinase C (PKC) which regulates various activities via protein phosphorylation

Excitotoxicity is postulated to account for several acute (e.g. stroke) and chronic (e.g. negative symptoms of schizophrenia) forms of brain malfunction. Excess glutamate activity allows too much calcium to enter the cell and activate enzymes that in turn produce free radicals that destroy membranes and organelles.

Attempts are afoot to prevent such pathological changes by using glutamate (especially NMDA) antagonists, free radical scavengers⁷²⁹, or enzyme blockers⁷³⁰. (Graham & Hickey, 2002) Memantine, an NMDA receptor antagonist, is advocated for moderate to severe Alzheimer's Disease.

Clozapine, and perhaps other atypical antipsychotics such as olanzapine, may exert part of its therapeutic effect by increasing activity at the NMDA receptor. It blocks the psychotropic effects of ketamine.

Ketamine can induce a schizophrenia-like reaction and exacerbate the symptoms of schizophrenia.

Raclopride binding to D2 receptors is diminished by ketamine, which raises the possibility that ketamine causes striatal DA release. (Breier et al, 1998)

Glycine

⁷²² Term coined by J W Olney in connection with selective neurodegeneration in newborn rodents given monosodium glutamate.

⁷²³ N-methyl-D-aspartate.

⁷²⁴ α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

⁷²⁵ **Kainic acid**, a glutamic acid analogue derived from seaweed, is a powerful convulsive chemical.

⁷²⁶ Ionotropic.

⁷²⁷ **Regulation of the NMDA receptor** is complex with many sites of allosteric modulation, such as the glycine site. Agonists at the glycine site may be full (glycine, D-serine, and D-alanine) or partial (D-cycloserine). Cycloserine is an agonist at low concentrations and an antagonist at high concentrations. High-dose cycloserine used to treat TB may cause psychosis.

⁷²⁸ Loss of long GABA neurones connecting caudate to globus pallidus.

⁷²⁹ E.g. vitamin E and the so-called 'lazaroids'. Free radical scavengers bind reactive oxygen species. The main free radical species in humans are the hydroxyl (OH) and superoxide (O₂⁻) radicals and nitric oxide (NO).

⁷³⁰ E.g. caspase inhibitors, enzymes said to be involved in apoptosis.

Apart from GABA, glycine is the other main amino acid inhibitory NT, and is found in highest concentration in the spinal cord. Milacemide is converted to glycine in the CNS.

Histamine

Histamine, derived from L-histidine⁷³¹, is released from mast cells and causes vasodilation and activation of smooth muscle as well as gastric acid secretion. It mediates itch and pain. Posterior thalamic histaminergic neurones project axons throughout the CNS and are involved in wakefulness, appetite, and metabolic control. Histamine H1-3 receptors are found in the CNS and peripherally whereas H4 receptors are only found peripherally. H1 blockers include diphenhydramine (Benadryl) which can be used to treat drug-induced Parkinsonism or acute dystonia, or it can be employed for its hypnotic and anti-motion sickness properties⁷³². Cyproheptadine (Periactin) blocks H1 receptors and is an antagonist at 5-HT receptors. It has been used to put on weight in anorexia nervosa and, given before sexual intercourse, for inhibited orgasm in either sex due to SSRIs. Diphenhydramine and hydroxyzine have some antimuscarinic activity. H2 blockers like cimetidine are used for peptic disorders. Sedation and weight gain from antipsychotic drugs and antidepressants (e.g. mirtazepine) are antihistaminic effects. Based on animal studies suggesting that depletion of histamine affects short-term memories, researchers are examining the possibility of using H3 autoreceptor antagonists in patients with memory problems.

*Substance P*⁷³³

Although the brain is rich in substance P, it is mainly associated with the pain-conveying sensory afferents to the substantia gelatinosa of the dorsal horn. Release of substance P, which is inhibited by opiates, is associated with intense pain. Capsaicin, found in chili peppers, depletes substance P in nerve sensory terminals.

Neuropeptides

There are small proteins consisting of anything from two to dozens of amino acids. The physiological actions of neuropeptides last minutes to hours (v seconds to minutes for many other NTs) and they are found in picomolar to femtomolar concentrations (v nanomolar to micromolar for classical NTs and millimolar for glutamate). Peptide NTs coexist with other NTs, e.g. 5-HT coexists in neurones with substance P and enkephalin. While biogenic amines (e.g. DA) and amino acids (e.g. glycine) are manufactured at nerve terminals using enzymes from the cell body, peptides must be synthesised in the cell body itself. They are only deactivated outside the cell (by proteolysis), and have a long duration of action, their effects often persisting after they are degraded.

These peptides include cholecystokinin (CCK), vasoactive intestinal polypeptide (VIP, a member of the glucagon-secretin family), oxytocin, vasopressin (9 amino acids), TRH (3 amino acids), substance P (11-amino acid neurokinin peptide), bradykinin, galanin (30-amino acid neuropeptide; originally purified from colon and pituitary) stimulates growth hormone release; discovered in 1983), insulin, leu-enkephalin, and neurotensin. (Palkovits, 2002; Meyer, 2002) The co-existence of neuropeptides and classical NTs like 5-HT within the same neurone may be important for varying the effect of released NT and may have significance for understanding the effects of psychiatric somatherapies and mental illness. For example, TRH might act synergistically with serotonin to generate an increase in postsynaptic potential, while substance P may block postsynaptic autoreceptors, thereby inhibiting 5-HT release. Release of such peptides with serotonin appears to depend on an increase in electrical stimulation. (Hökfelt et al, 1987)

Cholecystokinin (CCK)⁷³⁴ is found in various forms, cholecystokinin octapeptide (CCK-8) probably being the most common variety in the central nervous system (CNS). CCK-8 and various analogues may modulate (regulate) CNS transmission in those DA neurones projecting to cerebral cortex and limbic system, but not those headed for the basal ganglia. These chemicals have been studied as possible antipsychotic agents, although with inconsistent results. An infusion of the tetrapeptide CCK-4 causes marked panic symptoms. Not surprisingly, therefore, cholecystokinin antagonists have also been looked at as potential anxiolytics.

Production of cocaine- and amphetamine-regulated transcript (CART) peptides is increased following use of either drug. They may play a role in drug abuse, control of stress and feeding behaviour.

⁷³¹ L-histidine is converted to histamine by L-histidine decarboxylase and histamine is broken down via oxidation or methylation.

⁷³² However, not all experts approve of Diphenhydramine as an hypnotic, pointing out that it causes confusion and sedation.

⁷³³ Gaddum and Von Euler discovered this excitatory transmitter in 1931.

⁷³⁴ A 33-amino acid neuroactive peptide co-transmitter with a variety of peripheral and central actions.

The main hypothalamic NTs stimulating feeding are (pancreatic) neuropeptide Y⁷³⁵, NA, opioids, galanin, and growth hormone releasing factor. Those inhibiting feeding include PYY (YY₃₋₃₆, PYY₃₋₃₆), CRF, serotonin, neurotensin, and CCK. (Gilbey & Macrae, 1993) It has been suggested that cholecystokinin (see above) and neurotensin receptor antagonists might have some antipsychotic activity.

α -melanocyte-stimulating hormone⁷³⁶ reduced food intake and increases energy expenditure by reacting with MC4R, a melanocortin⁷³⁷ receptor within the hypothalamus.⁷³⁸

PYY is a peptide secreted⁷³⁹ after a meal by endocrine L cells lining the distal small bowel and colon. In animal studies PYY inhibits hypothalamic neuropeptide Y-expressing neurones and agouti-related protein-expressing neurones via neuropeptide Y2 receptors, thereby disinhibiting nearby proopiomelanocortin-expressing neurones and decreasing food intake. PYY reduces fasting ghrelin levels in humans. (Batterham *et al.*, 2003)

Agouti-related peptide/protein (AgRP⁷⁴⁰)

This is produced in the arcuate nucleus of the hypothalamus. It increases appetite and reduces metabolism and energy loss.

Endogenous opioids (EOs)

These are peptide NTs. The precursor proopiomelanocortin (POMC) gives rise to ACTH, MSH, and β -endorphin. Proenkephalin gives rise to met-enkephalin and leu-enkephalin. Prodynorphin gives rise to β -neoendorphin and dynorphin. EOs act on 3 major receptors (μ , δ , κ) and are thought to be involved in the regulation of stress, pain and mood. Expression of the prodynorphin gene is controlled by a calcium-regulated transcription factor that binds to downstream regulatory element (DRE) of the gene and is known as DRE antagonistic modulator (DREAM).⁷⁴¹

Alpha-MSH (α -melanocyte stimulating hormone) is an anorectic peptide found in the arcuate nucleus. It decreases food intake. The mainly hypothalamic peptide melanin-concentrating hormone is important for feeding and energy balance because melanin-concentrating hormone knockout mice are thin, eat little and have increased rates of metabolic activity.

Purine receptors

Receptors for purines such as adenosine are divided into P1 and P2. P1 receptors are blocked by xanthines like caffeine and theophylline.

Monoamine oxidase

Monoamine oxidases, flavin-containing enzymes, occur as either MAO-A or MAO-B. MAO-A is found in brain⁷⁴², sympathetic nervous system, liver, and gut, whereas MAO-B is found in brain, liver, and platelets. MAO-A mainly acts on 5-HT and NA, but also on DA and tyramine. Tyramine may act as a false transmitter and displace NA from presynaptic storage granules. MAO-B mainly acts on phenylethylamine, but also on DA and tyramine. The classical MAOIs, such as tranylcypromine, irreversibly block MAO, whereas the reversible MAO-A inhibitors (RIMAs), like moclobemide, can be knocked off the enzyme by, for example, tyramine. SSRIs cannot be given for weeks⁷⁴³ after stopping a classical MAOI, but can be taken a week or so after stopping moclobemide.

MAO-B is inhibited irreversibly by selegiline, used with L-DOPA in the treatment of Parkinson's disease, with no dietary restrictions. At much higher doses selegiline inhibits both MAO A and B and has been used at such doses as an antidepressant. Selegiline is metabolised to a number of active compounds including

⁷³⁵ Often stated to be the most powerful stimulator for feeding, but **peptide YY** may be more powerful. (Halmi, 2003, p. 1002) Both arise in the pancreas. When injected into the paraventricular nucleus, **neuropeptide Y** increases intake of food and water.

⁷³⁶ Peptide carved from proopiomelanocortin.

⁷³⁷ Concerns have been raised about use of synthetic melanocortin analogues melanotan I and II (mimic alpha-MSH) which are reaching people without being subject to normal safety measures. (Evans-Brown *et al.*, 2009) They are used to produce a skin tan or to produce an erection. Melanotan II can cause hypertension in some people. Needle-sharing is a significant concern.

⁷³⁸ Deletion of the mouse Mc4r gene leads to hyperphagia, obesity, hyperphagia, hyperinsulinaemia and reduced energy expenditure. Mutations of the MC4R gene are reported in 3-7% of humans with a BMI greater than 40 and severe obesity commencing before the tenth birthday.

⁷³⁹ Proportionate to caloric intake.

⁷⁴⁰ The agouti is a rodent. AgRP resembles a protein (agouti signalling peptide) that gives colour to the body coat.

⁷⁴¹ When DREAM binds to DRE it inhibits transcription of the prodynorphin gene. DREAM knockout mice have been used to study regulation of nociception: such mice have a diminished response in neuropathic and inflammatory models of chronic pain. (Vogt, 2002)

⁷⁴² A PET radiotracer is available for MAO-A.

⁷⁴³ Depending on the particular SSRI.

methamphetamine, levoamphetamine, and N-desmethylselegiline. Toxic interactions with SSRIs have been recorded, although it may be safe with TCAs. (Brown et al, 2000) Sudden cessation of selegiline intake can cause nausea, hallucinations, and confusion. (Krishnan, 1998)

Rasagiline is another MAO-B inhibitor.

Pethidine (meperidine) can cause hypertension, hyperpyrexia and death if combined with a MAOI. Fava beans, which contain DA, have similar effects to tyramine in the presence of MAOIs. Tyramine is formed in foodstuffs by decarboxylation of tyrosine during aging, ripening or decay. The food containing the highest tyramine content is spoiled pickled herring. Aged cheese contains a high level of tyramine.

Catechol-o-methyl transferase (COMT)

COMT is a magnesium ion-dependent enzyme that catalyses the transfer of methyl groups from S-adenosyl methionine to a hydroxyl group of a catecholamine. The gene for COMT is at 22q11. COMT is involved in extracellular breakdown of catecholamines. The peripheral COMT inhibitor entacapone (Comtess – 200 mg with each dose of levodopa) is used to treat Parkinson's disease.⁷⁴⁴ It reduces levodopa breakdown before it reaches the brain. The dose of levodopa may be reduced if the patient takes entacapone. Side effects are mainly due to increased brain dopamine levels and include dyskinesia and nausea that may respond to dosage adjustment. Uncommonly, it can cause abdominal pain and diarrhoea. Another COMT inhibitor, tolcapone (Tasmar), may cause serious liver damage.

Monoamine reuptake inhibitors (MARIs)

This group contains such agents as TCAs, mianserin, trazodone, and the SSRIs. Trazodone is an antagonist at 5-HT₂ receptors. It also blocks postsynaptic alpha-1-adrenoceptors. On the other hand, its active metabolite, m-chlorophenylpiperazine (m-CPP), is a 5-HT receptor agonist.⁷⁴⁵

Mode of action of antidepressants: a critique

We tend to apply rationale for how a drug works after its benefits are noticed. (Duffin, 2000) The points against reuptake inhibition being therapeutic are that it occurs within hours whereas improvement in mood requires weeks, not all reuptake inhibitors are true antidepressants (e.g. amphetamine), and some effective antidepressants, such as trimipramine and bupropion, have negligible reuptake disinhibitory properties. On the other hand, the time required for an antidepressant drug to induce beta-adrenergic receptor downregulation⁷⁴⁶ closely parallels the course of clinical improvement. Beta-receptors are downregulated by TCAs, MAOIs, and ECT. Some antidepressants do not have this property, such as mianserin, trazodone, paroxetine, citalopram and fluoxetine. Also, shortening the time to downregulation does not accelerate clinical response, and β -receptor agonists like clenbuterol cause downregulation but are poor antidepressants.

Presynaptic α -2-autoreceptors are activated by NA in the synaptic cleft, causing inhibition of further NA release due to increased potassium conductance and consequent cellular hyperpolarisation. (Nutt, 1993) Antidepressants given long-term, lithium and ECT reduce the sensitivity of α -2-autoreceptors in platelets. However, deductions concerning depression ignore the fact that α -2-autoreceptors are both pre- and post-synaptic in the brain. (Trimble, 1996)

SSRIs block the serotonin transporter⁷⁴⁷, an effect that only takes a few hours, the activity of the serotonergic neurone recovering over the next 2 weeks. (De Montigny & Blier, 1985) Chronic SSRI dosing desensitises 5-HT_{1A} autoreceptors, but not 5-HT_{1A} receptors on postsynaptic cells. 5-HT₂ receptors may be upregulated in depression and downregulated by antidepressant drugs like SSRIs and TCAs. However, both antipsychotic drugs and LSD also downregulate these receptors, and ECT upregulates them!

⁷⁴⁴ Leonard (2003, p. 67) is not enthusiastic about COMT inhibitors because 'at most only 10% of the monoamines released from the nerve terminal are catabolized by this enzyme'.

⁷⁴⁵ See nefazodone.

⁷⁴⁶ Decreased receptor number or sensitivity.

⁷⁴⁷ The **serotonin transporter** is a cell membrane protein (gene [SERT] on chromosome 17) involved in the recycling of 5-HT, thereby terminating the synaptic activity of serotonin. Polymorphisms (number of tandem repeats) may explain a connection between depression and anxiety. (Ohara et al, 1999) The long (L) variant of SERT contains a 44-bp sequence which the short (S) variant does not possess. The L-variant generates more mRNA and hence more protein and thereby increases synaptic transport so that duration and intensity of 5-HT neurotransmission are diminished. The S-variant is thought to be involved in the origin of depression and anxiety. It is important to note that the binding potential of the 5-HT transporter varies with the seasons – higher 5-HT transporter density is associated with lower synaptic 5-HT levels. (Praschak-Rieder et al, 2008) This fact may have explanatory power concerning seasonal changes in normal and abnormal behaviours.

All chronic antidepressant treatments appear to increase intracellular concentrations of cAMP response element binding (CREB) protein as well as cAMP-dependent protein kinases. CREB may be responsible for receptor protein up- and downregulation. Two to 3 weeks are required for induction of CREB, which fits with time to clinical response. (Musselman *et al.*, 1998)

Nitrous oxide (N₂O/laughing gas): this euphoriant can cause delirium acutely. Chronic exposure can lead to combined degeneration of the posterior and lateral columns of the spinal cord (similar to B12 deficiency).

*Nitric oxide (NO)*⁷⁴⁸

NO, known as 'endothelial relaxing factor' before elucidation of its true nature, is an NT without specific receptors. It is not stored, is manufactured on demand, and is released by simple diffusion. Penile neurones and other tissues, such as granule cells in the cerebellum and some other brain cells, contain nitric oxide synthetase (NOS) which makes NO from l-arginine, leaving l-citrulline as a by-product. NO then diffuses to adjacent neurones or smooth muscle and leads to the formation of cyclic guanosine monophosphate (cGMP) by activating guanylyl cyclase (GC). NO binds to the heme (iron) site on GC. Glutamate and calcium can trigger NOS to form NO.

cGMP relaxes smooth muscle, thereby opening blood vessels and leading to penile erection. cGMP is terminated by phosphodiesterases (PDEs), of which there are several forms, the one in the penis being type five (PDE V). NO is also involved in the smooth muscle of the heart's blood supply (mediating the action of nitroglycerin), in blood pressure control, in platelet aggregation, and in peristalsis. NO may act as a retrograde transmitter in the CNS, being part of the back talk from post- to pre-synaptic neurones. It may also have a role in memory, plasticity of nerve cells, and neurotoxicity (NO is a free radical and its combination with O₂ increases its toxicity).

Inhibiting PDE V with sildenafil (Viagra) can decrease the rate of destruction of cGMP. Sildenafil only produces an erection if one is mentally interested in having sex, unlike, for example, the prostaglandin alprostadil which also relaxes smooth muscle to produce an erection, but in this case irrespective of whether the individual is currently interested in having sex or not.

NO appears to have a diversity of roles in the body, e.g. learning and memory (longterm potentiation in the hippocampus) and it may inhibit maternal behaviour in rats by modulating oxytocin release.

Carbon monoxide

This is produced in the brain by haemeoxygenase-2, an enzyme present throughout the brain but particularly common in the olfactory system, cerebellar Purkinje cells, and hippocampal pyramidal cells. It is freely diffusible and, like NO, it activates guanylyl cyclase.

*Attention deficit disorder (ADD)*⁷⁴⁹

It is postulated that the poor attention skills may be due to underactivity in DA and NA pathways innervating the prefrontal cortex (PFC), whereas hyperactivity⁷⁵⁰/impulsivity may be mediated by the dopaminergic neurones of the nigrostriatal pathway.

Medications for attentional difficulties include pemoline⁷⁵¹, which has caused liver toxicity, sometimes fatal. (Cozza *et al.*, 2003, pp. 1405 & 1407) Amphetamines are more popular in America. L-amphetamine is the enantiomer (Leonard, 2004) of d-amphetamine. L-amphetamine releases both DA and NA, whereas d-amphetamines releases DA only. Low doses of amphetamine improve attention in such cases. Some cases may respond best to a mixture of l- and d-amphetamine. Methylphenidate, which increases DA availability, is also employed in treating this problem. It has a slower onset of action but lasts longer than amphetamine. Postsynaptic α -2 agonists, such as clonidine, may be beneficial. Bupropion, which is chemically related to amphetamine and can cause seizures in high doses, increases the availability of DA and NA, helps some cases.

In cases of hyperactivity/impulsivity, increasing DA levels may paradoxically produce a calming effect. It has been suggested that cortically derived glutamate reduces impulsivity by inhibitory actions in the striatum. Higher doses of stimulants are effective for hyperactivity/impulsivity than are needed for attentional problems.

⁷⁴⁸ This should not be confused with nitrous oxide.

⁷⁴⁹ This 'complex' of symptoms has had many names: hyperkinetic disorder, hyperactivity-ADD, and ADD depending on the symptoms expressed.

⁷⁵⁰ Hyperkinesis.

⁷⁵¹ Withdrawn in UK.

Concerns have been expressed about the scope of the diagnosis on the one hand and about missing the diagnosis in both children and adults. Since stimulants can lead to tolerance, escalating doses and abuse outside core ADD, great care is required on the part of physicians. These considerations do not appear to apply to the core group. DSM-IV demands that symptoms of ADD go back to before age 7 years. Cynics would say that the overlap between ADD and conduct disorder has led to pressure from relatives and solicitors to diagnose adult ADD where dissociality once reigned!

Ethyl alcohol

Alcohol is metabolised to CO₂ and H₂O in 3 main oxidative stages. Firstly, ethyl alcohol (C₂H₅OH) is converted to acetaldehyde (CH₃CHO) in the presence of alcohol dehydrogenase; then acetaldehyde is changed to acetic acid (CH₃COOH) by aldehyde dehydrogenase; and, finally, acetic acid, having been converted to acetyl coenzyme A, enters the tricarboxylic acid cycle to be degraded to CO₂ and H₂O. Disulfiram inhibits the action of aldehyde dehydrogenase with resultant acetaldehyde accumulation. Acetaldehyde causes histamine release. Interestingly, alcohol dependent people develop higher acetaldehyde levels than their non-dependent comparators when they drink. This acetaldehyde interacts with catecholamines to produce complexes called tetrahydroisoquinolines that bind to specific brain receptor sites. Since tetrahydroisoquinolines resemble morphine alkaloids in structure, the theory has arisen that this may be a mechanism that stimulates further drinking. Disulfiram also inhibits dopamine hydroxylase and may potentially exacerbate schizophrenia.

The active absorption of water-soluble forms of vitamin B1 by the intestine is inhibited by alcohol. It is therefore better to employ passively absorbed fat-soluble forms such as thiamine propyldisulphide. (Madden, 1985) Absorbed thiamine is converted to thiamine pyrophosphate, the active form. The latter is a coenzyme for transketolase (involved in hexose monophosphate shunt pathway). Some people inherit a form of transketolase that has less affinity for activated thiamine and may develop Wernicke's encephalopathy with relatively mild lack of B1.

Alcohol dehydrogenase is absent during early embryonic life, making the foetus more susceptible to alcohol's effects on cellular proliferation, an effect demonstrable in mice deficient in this enzyme. Alcohol increases inhibitory neurotransmission at GABA A receptors, reduces inhibitory neurotransmission at the NMDA subtype of glutamate receptors, and possibly also releases opiates and endocannabinoids. Acamprosate (calcium bisacetylmotaurinate; Campral EC), which reduces craving for alcohol, seems to act either by stimulating GABAergic inhibitory neurotransmission or by postsynaptic antagonism of excitatory amino acids, especially glutamic acid. The latter mechanism is favoured by Sass et al. (1996) Congeners are substances in alcohol other than ethyl alcohol, including other alcohols and acetaldehyde. They are thought to be psychoactive, although their clinical effects require clarification.

Cannabis

The brain has its own cannabinoid receptors: CB1 in CNS and peripheral nervous system (G-protein coupled and also modulates adenylate cyclase and ion channels) and CB2 (chiefly in the immune system). An endogenous cannabinoid system activates these receptors. Endocannabinoids⁷⁵² are manufactured in neurones and taken up and destroyed by both neurones and glia. THC mimics their actions.

Endocannabinoid actions at CB1 are antagonised by SR141716. The latter substance has been shown to block the acute psychological and physiological effects of smoked marijuana without altering THC pharmacokinetics. (Huestis et al, 2001) AM404 is an anandamide transporter inhibitor.

Anandamide activated vanilloid (resiniferatoxin) receptors within cells, which may explain its effects on pain transmission. (Mayfield et al, 2003, p. 847)

Gamma-glutamyl transferase (γ-GT)

Increased plasma activity of this microsomal enzyme is a sensitive index of hepatic abnormality. Causes of such increased activity include biliary obstruction (producing highest increase), parenchymal damage for any reason, and microsomal enzyme induction due to alcohol (a γ-GT normal level does not outweigh excess intake of alcohol), carbamazepine, phenytoin, primidone, barbiturates, glutethimide, meprobamate, rifampicin, or griseofulvin.

Growth factors

⁷⁵² Such as the ethanolamide fatty acid anandamide. (Sanskrit: *ananda*, bliss) Independent of cannabis use, levels of the endogenous cannabinoid anandamide were found to be elevated in the blood and CSF of patients with schizophrenia.

Peptide regulatory factors are important for nervous system development and in neurodegenerative disorders for restoring neural circuits and coordinating glial response to damage. The best known is nerve growth factor (NGF). NGF mediates the differentiation and survival of nerve cells. Cholinergic nerve cells in nucleus basalis of Meynert, the medial septum and the striatum express both NGF receptors⁷⁵³, i.e. tropomyosin-related kinase A (TrkA) and p75, and NGF may help to maintain the function of these nerve cells. CNS growth factors may prove useful in the future, such as in facilitating regeneration following trauma, and in retarding or reversing age- or disease-related neural degeneration. (Logan, 1990)

Leptin

Obesity may be related to leptin⁷⁵⁴ (an adipokine) resistance: leptin levels are chronically increased in obese humans⁷⁵⁵ and decreased during starvation. (Gomez ea, 2002) Leptin levels in plasma and CSF are significantly reduced in underweight patients with anorexia nervosa, rising to normal values with weight restoration. (Halmi, 2003, p. 1003) Leptin, a 146-amino acid protein that is one of the interleukin 6 cytokines, is produced by fat cells and reduces food intake, decreases insulin levels, and lowers blood glucose concentration in the ob/ob (obese – lacks functional leptin) mouse but not in the db/db (mutant diabetic – lacks leptin receptor) mouse. (Bray, 1996; Caro ea, 1996; Schwartz ea, 1996) Giving exogenous leptin will reduce food intake and weight whether endogenous leptin is normal or deficient. Leptin concentration is proportional to fat mass when energy balance is stable. Acute fasting causes a larger fall in leptin levels than would be expected from any change in fat mass and excessive food intake leads to enhanced rise in circulating leptin following the meal. A fall in leptin levels signal a smaller fat mass and this leads to an increase in appetite. Insulin exerts a delayed stimulatory action on leptin production in adipocytes. Leptin may exert its central effects by inhibiting activity of neurones containing neuropeptide Y and agouti-related peptide and stimulating MSH activity. It is thought that leptin levels increase during atypical antipsychotic drug treatment as a result of increased weight rather than by any direct effect of these drugs on leptin physiology. (Hua ea, 2008)

Ghrelin

Ghrelin⁷⁵⁶ stimulates feeding and produces obesity in rodents. Levels of ghrelin rise just before a meal and with restricted food intake (including starvation⁷⁵⁷) and fall quickly following a meal. (Cummings ea, 2002) Bulimic patients may have blunted ghrelin response to a meal. (Monteleone ea, 2003) It acts on the hypothalamus. An infusion of ghrelin causes a brief increase in hunger in humans. There is preliminary evidence that ghrelin levels increase during atypical antipsychotic drug treatment. (Hua ea, 2008) Because obesity is associated with decreased ghrelin levels, it is unlikely that ghrelin causes obesity. Weight loss following gastric bypass surgery, unlike dieting-induced weight loss, is associated with decreased ghrelin levels that do not rise before a meal. Much more work needs to be done before a role for ghrelin antagonists in the management of obesity can be clarified either way.

Ghrelin and leptin

Hypothalamus detects *ghrelin* from stomach → hunger

Hypothalamus detects *leptin* from adipose tissue → satiety

Adiponectin

This 244-amino acid protein is secreted exclusively by adipose tissue and levels are low in the obese, i.e. adiponectin levels in humans negatively correlate with body weight and insulin levels. It is important in regulation of glucose levels, the breakdown of fatty acids, and sensitivity to insulin.

Ginkgo biloba

Ginkgo biloba, an over the counter (OTC⁷⁵⁸) preparation, is made from the leaves of the ginkgo or maidenhair tree. An antioxidant effect has been suggested. Combination with drugs that increase the risk of

⁷⁵³ Neurotrophic factors (neurotrophins) activate Trk (A, B, and C subtypes) and p75 transmembrane (which binds mature and precursor molecules) receptors.

⁷⁵⁴ Gk. *leptos*, thin.

⁷⁵⁵ Leptin levels are increased in *obstructive sleep apnoea* over and above levels found in obese controls. (Ip ea, 2000)

⁷⁵⁶ A 28-amino acid peptide produced by oxyntic cells in the gastric fundus. It gets its name because one of its actions is to cause **growth hormone release**.

⁷⁵⁷ Ghrelin levels are increased in underweight patients with AN and then fall as weight increases. There is a negative correlation between BMI and ghrelin levels.

⁷⁵⁸ The popularity of OTC preparations has a long history. (Digby, 1999, p. 228)

bleeding may be dangerous as ginkgo antagonises platelet activating factor. Ginkgo can cause headache, gastrointestinal upset, and rashes. Claims for beneficial effects on normal memory or in preventing dementia in the elderly have not received scientific support.(Frankish, 2002; DeKosky ea, 2008)

Neurochemical/molecular biological terms

Amyloid in Alzheimer's disease (animal research): Changiz Geula and others injected fibrillar B amyloid into (especially older) primate (more than rat) brain leads to cell loss with an intense microglial reaction at the injection site. There is also induction of hyperphosphorylated tau, the protein forming neurofibrillary tangles in Alzheimer brains.(Berger, 1998) β -amyloid protein is produced by cleavage of the precursor protein by secretases. Gamma-secretase produces the carboxyl terminus of beta-amyloid protein, the length of this terminus influencing the pathogenic effects of the protein. Research aims at producing inhibitors of gamma-secretase.(de Deyn, 2002)

Apolipoprotein E (Apo E): 299 amino acid compound found in serum and CSF. Major component of circulating lipoproteins and important regulator of lipid metabolism. Has a crucial role in cholesterol metabolism. Exists in 3 major isoforms (E2, E3, the commonest, and E4) encoded by 3 alleles (E2, E3, and E4) of the apolipoprotein E gene. Two functional domains, one end binding to cholesterol and the other to cellular low-density lipoprotein (LDL) and other receptors for lipids, thereby facilitating endocytosis. Apo-E2 cannot bind LDL receptors and is important in coronary artery disease and strokes. Apo-E4 is important in the pathogenesis of late-onset Alzheimer's disease. In an autopsy study (Polvikoski ea, 1995) the E4 allele of apolipoprotein E was significantly associated with Alzheimer's disease. Dementia is latest in onset with no E4 allele, earlier with one E4 allele, and earlier still with two such alleles.(Devasenapathy & Hachinski, 1997) Even in elderly subjects without dementia, the apolipoprotein E genotype is related to the degree of deposition of β -amyloid protein in the cerebral cortex. The E4 allele of Apo E is on chromosome 19 [q13]. Apo E plasma levels were found to be significantly reduced in treatment-free patients with schizophrenia spectrum disorder and those with bipolar disorder, levels increasing with treatment in the bipolar patients.(Dean ea, 2008)

Cytoskeleton: This gives the neurone its shape and allows for the traffic of proteins and organelles within various parts of the neurone). There are three main fibrous components: microtubules (transport highways for organelles made up of tubulin subunits extending in bundles throughout the neurone to form a scaffold – stability is provided by microtubule-associated proteins [MAPs]), neurofilaments (very stable and abundant in axons, these form part of neurofibrillary tangles), and actin⁷⁵⁹ (a dense network beneath the neuronal membrane and, together with various binding proteins, is important for cell motility, synaptic specialisation, and axon and dendrite plasticity.

G-proteins: family of guanosine triphosphate binding proteins that play an obligatory role in the transduction of a wide range of extracellular, receptor-detected signals across cell membranes to intracellular effectors (NT + receptor + G-protein activate protein kinase); they couple receptors to effectors. Lithium may exert some of its therapeutic actions via G-proteins.

Imidazoline receptors: newly discovered; some of these, like $\alpha 2$ -receptors, have a presynaptic inhibitory effect on NA release; they might have a role in depression.

Myo-inositol: Precursor of phosphorylated inositols involved in phosphatidyl inositol⁷⁶⁰ intracellular signalling pathway. Dephosphorylation of inositol triphosphate yields myo-inositol, which becomes incorporated in phosphatidyl inositol. When a neurotransmitter bind to its receptor, phosphatidyl inositol is further phosphorylated to again yield inositol triphosphate.

Second messengers: these activate specific types of protein kinase that regulate the phosphorylation state of numerous substrate proteins (third messengers) which act as transcription factors regulating trans-synaptic gene expression.

Signal transduction: processes by which effects of NT binding to receptors produce alterations in neural functioning; G-proteins are examples of signal transducers.

Tau: one of a family of microtubule-associated proteins that functions to stabilise polymers of tubulin⁷⁶¹; 6 isoforms⁷⁶² (produced by differential splicing of the same gene) splicing of tau are known; abundant in

⁷⁵⁹ The same contractile protein as that found in muscle.

⁷⁶⁰ Inositol is a glucose isomer and myo-inositol (q.v.) is the most common inositol isomer in the mammalian CNS.

⁷⁶¹ Microtubules, polymers of tubulin, are involved during mitosis in transport within the cell are in guiding chromosomes to daughter cells, whereas after mitosis they have a transport function only.

neural tissue, predominantly in axons; decreased concentration of soluble tau protein occurs in old age, even in the absence of dementia.(Garruto & Brown, 1994) Exists in CNS as 6 isoforms generated from a single gene. Aberrant phosphorylation of tau protein is associated with paired helical filaments, the main structural element of neurofibrillary tangles. In other words, the central component of neurofibrillary tangles is a cytoskeletal protein called tau, modified by abnormal phosphorylation. Different neurodegenerative conditions associated with tau can be differentiated on Western blots, e.g. bands of 60 and 64 kDa phosphorylated tau in Pick's disease.

Tribulin: proposed name for an endogenous anxiolytic substance within the brain.(Sandler, 1983) This low molecular weight substance was isolated from human urine. It inhibits binding of the BZD to its receptor site. **Other proposed endogenous BZD receptor ligands** (*endozepines*) include nicotinamide, inosine, hypoxanthine (the latter three molecules may have mixed agonist-antagonist properties; the latter two may modulate BZD receptors by activating purinergic mechanisms), ethyl- β -carboline-3 carboxylate, nephentin (large polypeptide, found in bile ducts and other peripheral tissues and to a lesser extent in brain – possibly gives rise to another chemical that acts on BZD receptor), diazepam-displacing activity in human CSF, and the anxiogenic diazepam-binding inhibitor (DBI; Leonard, 1997; an 86 amino acid peptide that can be spliced into biologically active fragments) which inhibits binding of tritiated diazepam (as well as antagonists and inverse agonists) to the BZD receptor. Leonard(2003, p. 234) emphasised the controversial nature of speculation in this area and informs us that BZDs may exist in plants (e.g. potato) and in the brains of mammals. 'Idiopathic recurring stupor'⁷⁶³ may be due to an excess of endozepines. It can be interrupted (quickly and temporarily) by flumazenil injections.(Rothstein ea, 1992)

Extrapyramidal side-effects (EPS)

Dopaminergic neurones projecting from the substantia nigra to the corpus striatum exert an inhibitory action on cholinergic striatal cells. The latter, in turn, inhibit striatal GABAergic neurones that are themselves inhibitory for the dopaminergic neurones of the substantia nigra, thus completing a circuit. If Ach and DA actions are blocked simultaneously, then the effects on the motor system are cancelled out. However, if the Ach system is freed from DA inhibition, then EPS emerge.

The TCA blocks D2 receptors and causes EPS.(Rudorfer & Potter, 1989) SSRIs can also cause EPS.

Inborn errors of metabolism

Most enzymes can have activity levels of less than half of normal without serious consequences, a fact that allows one to test for heterozygous carriers. When two heterozygous carriers of a recessive gene mate one in four offspring will be homozygous and manifest the associated disorder. Incestuous relationships and cousin marriages carry the highest risk of this happening.

Phenylalanine can be converted to σ tyrosine and thence to σ hydroxyphenylacetic acid, or to phenylpyruvate and NH_3 , the phenylpyruvate being metabolised to phenylacetate and phenylactate, or to tyrosine by an hydroxylase enzyme (step A). Tyrosine can be converted to DOPA or to adrenaline via dopamine and noradrenaline, or it can be changed to p-hydroxyphenylpyruvate; the latter is changed to homogentisate by an oxidase enzyme (step B) and on to maleylacetoacetate by further oxidation (step C), and finally to fumarate and acetoacetate. Phenylketonuria⁷⁶⁴, tyrosinosis and alcaptonuria result from enzymatic defects at steps A, B and C respectively. The metabolites σ hydroxyphenylacetic acid, phenylacetate and phenylactate are excreted in phenylketonuria.

Regarding the sulphur-containing amino acids, homocysteine can be converted into or from homocystine and methionine, or can be changed into cystathionine (a normal brain constituent; step 1) and thence cysteine (step 2). A defect at step 1 leads to homocystinuria,⁷⁶⁵ while one at step 2 leads to cystathionuria.

⁷⁶² These isoforms may have 3 (= 3R, found mainly in Pick's disease) or 4 (= 4R, found in corticobasal degeneration and progressive supranuclear palsy) or zero microtubule-binding domains. They may have 1 or 2 N-terminal inserts.

⁷⁶³ Frequent or infrequent attacks of stupor/coma lasting hours/days with diffuse 13-18 Hz activity on EEG and excess endozepine 4 in blood and CSF, mainly in males, average age of onset being in late 40s.

⁷⁶⁴ **Phenylketonuria (PKU)**: The incidence of PKU is 1 in 20,000. There is phenylalanine hydroxylase deficiency and phenylpyruvate and its derivatives are excreted in the urine. Cerebral damage is associated with intellectual disability and epilepsy. PKU is managed by avoiding phenylalanine in the diet (especially in the first months of life) and by giving tyrosine supplements.

⁷⁶⁵ **Homocystinuria** is an autosomal recessive disorder with lack of hepatic cystathione synthetases due to mutations in the cystathione-beta-synthetase gene at 21q22.3. Ectopia lentis, enlarged joints, hair that is fine and fair, skeletal abnormalities, cardiovascular disease (thrombo-embolism), emotional instability, with or without intellectual disability. Treat by restricting methionine intake.

Homocysteine, a simple amino acid, is said to be a risk factor for atherosclerotic disease, and possibly dementia as well. There is some evidence for a role for low and high homocysteine levels in depression⁷⁶⁶ and schizophrenia, respectively. (Sachdev ea, 2005; Neeman ea, 2005; Kim ea, 2008) Levels increase with age. It is a central metabolic intermediate in the metabolism of sulphur-containing amino acids, and⁷⁶⁷ it can be converted to either methionine or cysteine. Elevated plasma levels of homocysteine increases the risk of disease in coronary, carotid and peripheral blood vessels. Homocysteine might cause oxidative damage to vessel walls, proliferation of vascular cells, and promote the development of a prothrombotic state. There are a number of ways in which homocysteine might lead to dementia: cerebral micro-angiopathy, endothelial dysfunction, oxidative stress, and enhancement of beta-amyloid peptide-dependent neurotoxicity and neuronal apoptosis. Elevated plasma homocysteine levels have reported in young male patients with chronic schizophrenia. (Levine ea, 2002) Homocysteic acid, a metabolite of homocysteine, can cause neuronal excitotoxicity by stimulating NMDA receptors. Taking a normal diet and large doses of folate, vitamin B12 or betaine will usually reduce plasma homocysteine levels. Deficiency of folate or B12 causes reduced activity of methionine synthetase with an increase in homocysteine and a reduction in the formation of S-adenosyl methionine. There is some evidence that deficiency of these vitamins may be associated with a poor response to treatment for depression⁷⁶⁸ and that correction of such deficiencies may improve responsiveness. (Gottfries & Karlsson, 1997, p. 22)

Regarding those inborn errors of metabolism involving the Krebs-Henseleit cycle (which converts ammonia to urea), defects may occur at the points of conversion of carbonyl aspartate to citrulline (hyperammonaemia), the metabolism of citrulline to arginosuccinate in the presence of aspartate (citrullinaemia), and when arginosuccinate is changed to fumarate and arginine (arginosuccinic aciduria), all leading to disorders characterised by intellectual disability, cerebellar ataxia, poor muscle co-ordination, and, in some cases, seizures.

Psychopharmacology

'Psychopharmacology is a mixture of science and marketing, and the onus is on clinicians to be thoughtfully skeptical'. (Ghaemi, 2003, p. 123)

The *therapeutic index* (relative safety) of a drug refers to the gap between the therapeutic and toxic doses of that drug. A narrow index (as with lithium) suggests that careful prescribing and regular monitoring of levels in appropriate body fluids is required. ED₅₀ is the drug dose producing the wanted effect in half the subjects receiving the drug while the LD₅₀ is the dose that will kill 50% of people who receive the same drug. LD₅₀/ED₅₀ = therapeutic index.

Various markers of vulnerability to depression have been described: a possible increase in platelet MAO B, a decrease in CSF 5-HIAA, reduced platelet ³H-imipramine binding, possibly increased platelet α -2 adrenergic density, decreased platelet ³H 5-HT uptake, increased lymphocyte beta-adrenoreceptor density, diminished platelet 5-HT induced aggregation, increased 5-HT₂ receptor density, and delayed induction of early REM sleep phase by the muscarinic agent arecholine.⁷⁶⁹

Antidepressants are actually system stabilisers and require time to carry out their wanted actions. They may exert their effects presynaptically⁷⁷⁰ or postsynaptically⁷⁷¹.

Schizophrenia and lipid metabolism

Two polyunsaturated fatty acids (PUFAs) are essential in humans: linoleic and α -linolenic acids.⁷⁷² Levels of arachidonic acid in the frontal lobes, platelet conversion of arachidonic acid to prostaglandins, red cell

⁷⁶⁶ Perhaps high levels of homocysteine cause cerebrovascular disease and neurotransmitter deficiency, leading to depressed mood. (Folstein ea, 2007)

⁷⁶⁷ At the intersection of the re-methylation and trans-sulphuration pathways.

⁷⁶⁸ Jacka ea (2010), in a study of women, found that a traditional (wholesome) diet was associated with a lower likelihood of anxiety and depression than was a 'western' (fried/refined/sugary and beer) diet but direction of causality makes interpretation difficult.

⁷⁶⁹ Arecholine is contained in the betel nut [*Areca catechu*] which is commonly chewed by schizophrenic patients in developing countries, with some claims for a beneficial effect on positive and negative symptoms, but it is a factor in the development of oropharyngeal carcinoma. (Kurupparachchi & Williams, 2003)

⁷⁷⁰ Synthesis, release, metabolism or uptake of NTs.

⁷⁷¹ Recognition sites/receptors; transducers: G-proteins that couple a receptor to a secondary messenger; secondary messengers, such as cyclases and the PI system; function, such as at ion channels.

⁷⁷² PUFAs are stored in membrane phospholipids, are released by phospholipase A2 and related enzymes and act as precursors for a variety of chemicals such as prostaglandins.

membrane arachidonic acid and docosahexaenoic acid, and platelet membrane PUFA are reduced in schizophrenia. Brain phosphodiester concentration is increased in first episode cases, which may relate to increased breakdown of phospholipase A2. Phosphomonoesters are less plentiful, possibly due to decreased synthesis of phospholipids.

Phospholipase A2 is the rate-limiting enzyme in prostaglandin synthesis. It catalyses the release of PUFAs from phospholipids and is involved in synaptic outgrowth. Calcium-independent phospholipase A2 activity is increased in schizophrenia, whereas calcium-dependent activity is normal. In late childhood/early adolescence a normal pruning in synaptic density occurs. It is possible that increased phospholipase A2 activity could cause this process to fail. Furthermore, an abnormal gene in schizophrenia for phospholipase A2 has been postulated.

Lipid peroxidase and vitamin E concentrations are increased in schizophrenia, more so if patients smoke. In cancer, endogenous reactive oxygen species released during normal respiration damage nucleic acids and lipids. Because of this, it has been speculated that PUFA and antioxidant supplements might be beneficial in schizophrenia, perhaps in the form of eicosapentaenoic acid. However, supplementation with this last omega-3 fatty acid⁷⁷³ (Miyamoto *et al.*, 2002, p. 795) was ineffective in a trial conducted by Fenton *et al.* (2001). Nevertheless, Amminger *et al.* (2010) reported that long-chain omega-3 fatty acids⁷⁷⁴ may prevent the development of full-blown psychosis in young people with subthreshold psychotic states.

Polymeropoulos *et al.* (2009) studied the expression profile of over 12 thousand human genes in a cell treated with various antipsychotic drugs and compared the results to a library of other compounds employed in the treatment of other conditions. There was a common effect of antipsychotics on biosynthesis and regulation of fatty acids and cholesterol leading the authors to wonder if changes in lipid homeostasis might underlie the pathogenesis of schizophrenia: antipsychotics not only activated genes involved in lipid homeostasis but they did so preferentially from all other genes. Polymeropoulos *et al.* (2009) suggested that antipsychotics alter the ratio of polyunsaturated to saturated fatty acids and cholesterol content, which modulates fluidity of neuronal membranes and the membranes of surrounding cells. The end result could be changes in neuronal connectivity.

There is some preliminary evidence that eicosapentaenoic acid may augment antidepressant efficacy in major depression, (Nemets *et al.*, 2002) although dosage may be crucial. (Peet & Horrobin, 2002) Marangell *et al.* (2003a) found no significant effect for docosahexaenoic acid in subjects with major depression. According to Stoll *et al.* (1999) omega-3 fatty acids may have greater antidepressant than antimanic effects in bipolar disorder, and Noaghiul and Hibbeln (2003) suggest that greater seafood consumption reduces the prevalence of bipolar disorder. Frangou *et al.* (2006) reported the effective use of adjunctive ethyl-eicosapentaenoic acid in bipolar depression. Seafood and fish are rich dietary sources of eicosapentaenoic acid and docosahexaenoic acid. Miyake *et al.* (2006) failed to find a clear effect of dietary fish in preventing postpartum depression. Hallahan *et al.* (2007) reported a reduction in surrogate markers of suicidal behaviour and increased well-being in repetitive self-harmers receiving the long-chain omega-3 essential fatty acids eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA). Anonymous (2007b) concluded that omega-3 fatty acids should not be used on their own for treating depression⁷⁷⁵, but they *might* be helpful when added to existing antidepressant medication.

Breast milk, but not formula feeds, contains eicosapentaenoic and docosahexaenoic acids, leading Walker *et al.* (1999) to suggest improving nutrition in pregnancy and breast-feeding of the child. However, the association between breast-feeding and schizophrenia is tenuous. (O'Shea, 1997)⁷⁷⁶

Some factors involved in ageing

Genetic factors

⁷⁷³ Thought to be anti-inflammatory and perhaps to promote neurogenesis.

⁷⁷⁴ Given as concentrated marine fish oil.

⁷⁷⁵ Depressed patients were noted to have relatively low tissue concentrations of different components of the omega-3 pathway. There is some evidence to suggest that EPA may be the more effective agent in depression: DHA used alone may be ineffective and EPA is incorporated into body tissue quicker than is DHA. (Coryell, 2008, p. 518)

⁷⁷⁶ Similarly, breast-feeding does not improve intelligence in children. (Der *et al.*, 2006)

Contribute 25-33% of variance in human longevity (Bittles, 2008, p. 3)

Cell ageing

The Hayflick limit refers to the fact that cultured fibroblasts stop dividing after a certain number of divisions. The message to do so may be sited at the telomeric end of the chromosome, the latter region shortening each time a cell divides until a crucial length is reached.

Leucocyte telomeric length shortening may be reduced in patients with coronary artery disease by giving omega-3 fatty acids (Farzaneh-Far et al., 2010)

Oxidative stress

Free radicals (reactive oxygen species) overcome antioxidants leading to DNA mutations/deletions, affecting mitochondrial more than nuclear DNA⁷⁷⁷. Hastened by oxidative stress, protein and sugar react to produce glycosylation (protein glycation) with functional and structural damage to the protein.

Olive oil

The Mediterranean diet involves abundant use of olive oil, a rich source of monounsaturated fatty acids. There is some preliminary evidence that such a diet may help to prevent depression. (Sánchez-Villegas et al., 2009) One major limitation with this type of research is failure to control for a variable that might lead to both low depression levels and high consumption of certain culinary items (fish, olive oil, etc), e.g. active extended family networks.

Evening primrose oil

This treatment for premenstrual dysphoric disorder contains gamma-linolenic acid, an essential fatty acid precursor of prostaglandin E1 (PGE1). PGE1 is thought to decrease the effects of prolactin, the latter being one possible mechanism for premenstrual dysphoric disorder. Evidence of efficacy from randomised controlled trials have been negative. (Steiner & Yonkers, 1998, p. 15)

Some neuropathological phenomena

Necrosis follows acute ischaemia or trauma. Free radicals and excitotoxins⁷⁷⁸ are released.

*Apoptosis*⁷⁷⁹ is a normal regulatory mechanism but can be pathological (physiological v aberrant apoptosis). Acute cases occur around an area of necrosis (the penumbra). It affects individual cells that are removed by macrophages and adjacent cells. The apoptotic cell is small, round, and may be surrounded a halo that separate it from other cells; the cytoplasm is eosinophilic and the nucleus contains condensed chromatin. Programmed cell death⁷⁸⁰ is an analogous process that occurs in developing organisms and can be illustrated by the removal of webs between the digits. Caspases⁷⁸¹, cysteine-dependent, aspartate-specific proteases, are involved in apoptosis. These enzymes, which exist as procaspases (latent precursors) before activation, cleave other proteins, e.g. caspase 3 targets cytoskeletal proteins, DNA repair proteins, etc. Neuronal apoptosis is induced by beta-amyloid and mutated presenilins in Alzheimer's disease. Mutant huntingtin protein can cause neuronal apoptosis in Huntington's disease⁷⁸². The role of apoptosis in conditions such as schizophrenia⁷⁸³ requires further research. (Gaffney, 2002; Friedlander, 2003) BCL-2 is the human proto-oncogene on chromosome 18, the translocated locus in **B-cell leukaemia**. Bcl-2 proteins are involved in the response to apoptosis. Chronic lithium treatment increases Bcl-2 levels in rat brain and may be neuroprotective. (see Kessing et al., 2008)

Diaschisis is the idea that a lesion may influence brain regions far from the damaged area.

⁷⁷⁷ Numbers of mitochondria and their genomes vary with the tissue looked at, being high in muscle because of its high respiratory demand. There is an increase in random deletion of mtDNA with age. Voluntary muscle fibres have more mitochondrial electron transport problems as the organism ages. (Bittles, 2008, p. 10)

⁷⁷⁸ Glutamate, calcium, cytotoxic cytokines, etc.

⁷⁷⁹ Gk. dropping off of petals.

⁷⁸⁰ If cells didn't die in multicellular organisms tissue accumulation would reach astounding proportions! Apoptosis (shrinkage of cells), necrosis (swelling of cells), and possibly autophagy (starving cells eat their constituents) are the known modes of cellular demise. (Hotchkiss et al., 2009)

⁷⁸¹ Cysteine-requiring **aspartate protease**.

⁷⁸² Huntingtin is a protein associated with synaptic vesicles. It may trigger NMDA receptor-mediated excitotoxicity. Excitotoxicity is involved since injected excitatory amino acids mimic the pathology of Huntington's disease.

⁷⁸³ Reduced levels of the anti-apoptotic Bcl-2 family of proteins in schizophrenia and their increased levels with neuroleptic therapy.

Focal cortical dysplasia (FCD) consists of collections of large, bizarre neurones and 'grotesque' cells in cortex and underlying white matter. Clinical severity varies, the mildest degree consisting of microdysgenesis (neuronal heterotopias⁷⁸⁴, undulating cortical layers, or collections of nerve cells). Common manifestations of FCD are developmental delay, low IQ, seizures, and focal neurological deficits. *Hemimegalencephaly* is an abnormally big and dysplastic cerebral hemisphere, the opposite hemisphere being compressed. The affected hemisphere shows an enlarged and abnormally shaped lateral ventricle, hypertrophic white matter, and cortical dysgenesis. The cause is unknown but some cases have abnormal expression of L1CAM (L1 neural cell adhesion molecule), the latter having a regulatory role in neuroblast migration and the development of axons. Classical cases have developmental delay, hemiparesis, and intractable partial seizures from birth or infancy. Hemispherectomy may provide seizure control. Other manifestations include neurofibromata, hypomelanosis of Ito, epiloia, and linear nevus syndrome. *Hirano bodies* are small, eosinophilic rod- or carrot-shaped bodies that may be found in or close to pyramidal nerve cells of the hippocampus. They contain the microfilament protein actin and are numerous in Alzheimer's disease. *Holoprosencephaly*⁷⁸⁵ may involve non-separation of the cerebral hemispheres, a single midline eye, one nostril, and similar defects. Severe cases do not survive but mild cases may be represented by hypertelorism or a single incisor tooth occupying the midline. All degrees of intellectual disability have been reported. The majority of cases are due to chromosomal abnormalities. A number of genetic mutations have been described as underlying sporadic cases.⁷⁸⁶



Lewy body

Lewy bodies are laminated intracytoplasmic inclusion bodies in melanin containing neurones of the substantia nigra derived from the neuronal cytoskeleton. They are often seen in the remaining cells of the substantia nigra in Parkinson's disease. They can also be found in the pigmented cells of the locus coeruleus, dorsal vagal nucleus and reticular formation. On haematoxylin and eosin staining, substantia nigra Lewy bodies are pink, often with concentric rings and a surrounding colourless halo. Outside pigmented nuclei⁷⁸⁷ they may be amorphous. With the development of the concept of Lewy body dementia,(Q.V.) it has become clear that these eosinophilic intraneuronal inclusion bodies have a core of phosphorylated and non-phosphorylated neurofilament protein, microtubule protein, the protein ubiquitin⁷⁸⁸ and tau protein and can be found in cerebral cortex⁷⁸⁹. Antibodies to ubiquitin and α -synuclein⁷⁹⁰ can be used in postmortem tissue as a method of detecting Lewy bodies. The first genetic cause of Parkinson's disease was reported in 1997: a mis-sense mutation altering the fifty-third amino acid of the α -synuclein protein (A53T). Shortly thereafter, α -synuclein was found in Lewy bodies. Discovery of another mutation (A30P) followed. Genetic triplication⁷⁹¹ is associated with onset of Parkinson's disease and dementia with Lewy bodies in the mid-thirties. Genetic duplication⁷⁹² also leads to disease in some European families. Triplication is far more likely to be associated with dementia than is duplication.(Singleton & Gwinn-Hardy, 2004)

⁷⁸⁴ The neurones are not in their correct position.

⁷⁸⁵ Prosencephalon = forebrain.

⁷⁸⁶ E.g. sonic hedgehog or SHH gene (chromosome 7q.36).

⁷⁸⁷ Substantia nigra and locus coeruleus.

⁷⁸⁸ This is tagged on to other proteins so that they become degradation targets.

⁷⁸⁹ Temporal, hippocampal, cingulate, limbic and neocortical areas.

⁷⁹⁰ α -synuclein is normally present presynaptically and appears to be important for memory and learning.

⁷⁹¹ 3 copies of α -synuclein gene on one chromosome 4 and one copy on the other chromosome 4 = 4 genes.

⁷⁹² One extra copy of the α -synuclein gene = 3 genes.

Lissencephaly (a smooth brain: pachygyria and agyria⁷⁹³ and less cortical layers than normal) is a result of early disruption in cortical neuroblast generation. The severest cases involve the complete cortex with associated severe intellectual disability, paralysis, seizures, and cortical blindness. Mild cases involve small areas of cortex and may account for a significant proportion of childhood epilepsy. Mutation in the LIS1 gene⁷⁹⁴ is associated with Miller-Dicker syndrome⁷⁹⁵. Another form of lissencephaly is X-linked⁷⁹⁶, usually sporadic, sometimes familial, mainly affecting males (mild in females), with an inverted cortical neuronal lamination. Mutation of the RELN gene⁷⁹⁷ is found in the lissencephaly/cerebellar hypoplasia syndrome type-b.⁷⁹⁸

Necrosis is a response to noxae that kill adjacent tissues via inflammation and cicatrization.

Neurofibrillary tangles (NT) appear as coils of argentophilic⁷⁹⁹ tangled bundles. On electronmicroscopy, they are made up of paired helical filaments. The tangle is formed from tau protein itself derived from microtubules. Tau protein in Alzheimer's disease is abnormally phosphorylated by protein kinases, less soluble than normal, and unable to bind to microtubules. Glycogen synthase kinase-3 (GSK-3) is an important enzyme in this phosphorylation process. (Lovestone, 1997) Such abnormal phosphorylation of tau causes the neurofilaments to become cross linked and hence form insoluble complexes. (McKeith, 1997) Heavily phosphorylated tau does not bind to microtubules, leading the latter to collapse. Many affected neurones die and disappear in the latter stages of Alzheimer's disease, leaving *ghost/tombstone tangles*⁸⁰⁰. NTs are usually confined to the hippocampi in normal ageing, whereas in dementia they are more widespread and prevalent. NTs are found in almost every person surviving to the tenth decade.

NTs in Alzheimer brains abnormally express a fetal brain protein antigen known as Alz-50.

In association with NTs, the axonal processes emerging from neuronal soma contain neural thread protein that may be important in the repair and regeneration of neurones.

Periventricular nodular heterotopia consists of groups of cells in the wrong part of the correct tissue, in this case in the periventricular and subcortical white matter. There seems to be a failure of neurones to migrate to the cerebral cortex. There may or may not be other brain or other system anomalies. Females are affected more than males. Mutations in the FLNA gene on Xq have been reported⁸⁰¹. Seizures are the most common complication, and IQ is most often normal or somewhat lower than that.

Pick bodies are rounded, perinuclear condensations of straight (contrasting with helical Alzheimer) filaments found in cortical neurones. They contain cytoskeletal elements that bind polyclonal antibodies against neurotubules and a monoclonal antibody against neurofilaments.

Pick cells are cortical neurones that have been expanded and enlarged (ballooned) by argyrophilic bundles of neurofilaments.

Polymicrogyria consists of a cerebral cortex with excessive microscopic gyration. There are abnormal lamination of cortex with excess folding and fusion of gyri. Both perisylvian regions are affected in the commonest type. Most cases have epilepsy. X-linked cases have been described. Non-genetic causes include congenital cytomegalovirus infection, hypoxia, or reduced perfusion of the brain. Sometimes polymicrogyria may be part of a wider disorder, e.g. velocardiofacial syndrome.

Schizencephaly (developmental cortical clefts⁸⁰²) can arise as a result of focal ischaemia in the second trimester, cytomegalovirus infection, or, possibly, genetic mutations. Cavities may be open- or closed- (apposed walls) lipped. Open cases have seizures or hydrocephalus. Closed cases have motor delay or hemiparesis. There may be no septum pellicidum. Cases occur with hypoplasia of the optic nerves.

Senile (neuritic) plaques: a group of abnormal argyrophilic neuritic processes together with reactive microglia and astrocytes arranged in roughly spherical formation, with (mature plaque) or without

⁷⁹³ Pachygyria = broad, simple gyri; agyria = no gyri.

⁷⁹⁴ Chromosome 17p13.3 – protein product binds tubulin.

⁷⁹⁵ Severe intellectual disability, thick upper lip, upturned nose, high forehead, and lissencephaly.

⁷⁹⁶ Mutation at DCX or Doublecortin gene at Xq22.3-q23, its protein product also binding tubulin.

⁷⁹⁷ Human version of reelin in mutant reeler mouse, the latter suffering from a movement disorder.

⁷⁹⁸ Thick cortex, pachygyria, abnormal hippocampus, and hypoplastic cerebellum.

⁷⁹⁹ Plaques and tangles were stained with silver impregnation techniques. Immunostaining (using antibodies against important abnormal proteins) is the more modern approach.

⁸⁰⁰ Tangles without a neurone: especially common in hippocampus.

⁸⁰¹ A few cases are associated with abnormal 5p. Some others have microcephaly and autosomal recessive inheritance with ARFGEF2 gene (chromosome 20) mutation.

⁸⁰² If there is white matter or gliosis (T2 signal) then the diagnosis is more likely to be **porencephaly** (CSF-filled cysts due to destructive processes, e.g. infection or stroke).

(immature plaque) a core of extracellular amyloid. This amyloid is amyloid β -protein ($A\beta$, 39 to 43 amino acids), derived from a membrane-bound precursor, amyloid precursor protein (APP). The gene for amyloid precursor protein (APP) is on chromosome 21.⁸⁰³ Amyloid β -protein is a normal physiological product. It is hypothesised that amyloid β -protein deposition leads to tau phosphorylation, tangle formation and cell death: the so-called ‘amyloid cascade’. It has also been suggested that amyloid precursor protein gene mutations alone can account for all pathology found in Alzheimer’s disease. Senile plaques are found in 75% of people who reach their ninetieth birthday.

Subcortical band heterotopia (SBH, subcortical laminar heterotopia or ‘double cortex’) consists of bilateral bands of grey matter (disorganised neurones, better organised small neurones, and deeper nodules) lying between normal cortex and lateral ventricle and visible on MRI. Mutations in the DCX (X chromosome) and LIS1 (at 17p) genes have been described⁸⁰⁴. It is much more common in females. Seizures and mild to moderate intellectual disability are the typical features.

Prescribing during pregnancy and breast-feeding (O’Shea, 2001; Burt ea, 2001; Kohen, 2004; Yonkers, 2007)

‘There is rarely a valid reason to stop essential drug treatment during pregnancy’. (Kohen, 2004)

Maternal depression in early pregnancy is a risk factor for preterm delivery. (Li ea, 2008⁸⁰⁵) Webb ea (2008) examined a Danish population-based cohort and found a higher risk of fatal birth defect in the offspring of mothers (but not fathers) who had schizophrenia or affective disorder. This type of research does not say why this should be so: genes (and their interaction with environment), diet, smoking, alcohol, drugs (including medication), antenatal care issues, etc? King-Hele ea (2008) looked at live births and stillbirths over a 25-year period in Denmark. The offspring of mothers who had been admitted to hospital for mental illness at any time before the birth were at considerable risk of stillbirth and neonatal death; mothers with alcohol or substance dependence had an increased risk of stillbirth due to delivery complications; and women with affective disorders were more likely than comparison subjects to have stillborn babies with congenital abnormalities. Pregnant women in Taiwan with bipolar disorder are at increased risk for delivering low birth weight babies, preterm infants, and offspring who are ‘small-for-dates’ when compared with subjects who have no history of mental disorder. (Lee & Lin, 2010) Schizophrenia in either parent may be associated with increased likelihood of death of the baby. (Nilsson ea, 2008) In addition to the mother’s behaviour, poor social and parenting circumstances seem to be important. The untreated mentally disordered pregnant woman may neglect her diet, smoke, drink alcohol, abuse illicit substances, neglect personal and domestic hygiene, rarely take exercise, miss antenatal appointments, self-harm, and otherwise put herself and her unborn child at risk. Unfortunately, this scenario is not confined to the mentally ill. (Mc Millan ea, 2006) Maternal obesity⁸⁰⁶ may increase the risk of preterm births. (McDonald ea, 2010) The pregnant state is associated with reduced motility in and reduced emptying of the stomach. Volume of distribution is enlarged. Liver metabolism increases.⁸⁰⁷ Albumen levels fall. Drug binding capacity is diminished. Finally, the glomerular filtration rate is increased. Higher than usual doses of SSRIs or TCAs may be required to achieve remission from depression during pregnancy. Hepatic function and plasma protein binding are relatively low in the foetus, whereas cardiac output and blood-brain barrier permeability are relatively high. (Kohen, 2004) Medications may be available to the unborn via the placenta, and perhaps via the amniotic fluid. (Loughhead ea, 2006) Immature liver enzymes in premature babies places them at increased risk for adverse effects when exposed to drugs in maternal milk.

Adverse effects on fetus

⁸⁰³ q21; By way of contrast the genes for presenilins 1 and 2 are on chromosomes 14 [q24] and 1 [q31-42] respectively; like amyloid precursor protein, these are associated with early onset Alzheimer’s disease. Presenilins are gamma-secretases (aspartyl proteases) that cleave APP into the 42 amino acid version of amyloid peptide ($A\beta$ 1-42).

⁸⁰⁴ Males with mutations in DCX often have lissencephaly but affected females will have SBH.

⁸⁰⁵ This prospective cohort study also found that greater severity of depression increased the risk of preterm delivery and that the risk was exacerbated by low educational level, a history of fertility problems, and the presence of obesity and stressful events.

⁸⁰⁶ Maternal smoking may be a confounder.

⁸⁰⁷ The volumes of plasma and blood increase during pregnancy. Hepatic blood flow is unchanged. Therefore there is a fall in the proportion of cardiac output reaching the liver. As a result, metabolism of drugs may be affected.

- **Teratogenic** – first trimester exposure
- **Neonatal toxic and abstinence syndrome** – third trimester exposure
- **Behavioural/developmental** – evident later in childhood

The two best known drugs to be prescribed during pregnancy were the hypnotic thalidomide⁸⁰⁸, withdrawn in 1961, and diethylstilbestrol (DES – used to prevent miscarriage and later, in the USA, as a morning-after pill – associated with vaginal adenocarcinoma in young adult female offspring⁸⁰⁹). (Porter, 2002, p. 107)

The association between DES and malignancy is now in doubt. (Hollingworth, 2005, p. 772) Thalidomide⁸¹⁰ came back in use for the treatment of leprosy,⁸¹¹ multiple myeloma,⁸¹² multiple sclerosis, and wasting and aphthous ulcers in AIDS. Phenytoin, carbamazepine, sodium valproate, lithium, warfarin (dysmorphia and abnormal bone growth), carbimazole (neonatal hypothyroidism), retinoids (multiple anomalies), ACE inhibitors or antagonists (oligohydramnios), and danazol are commonly used teratogens. On the other hand, metoclopramide may be safe during the first trimester of pregnancy. (Matok ea, 2009a)

Dual diagnosis⁸¹³ is common. Females with schizophrenia are more likely to get married than males with the disorder, but, once married, males may have more offspring than their female co-sufferers, thus ensuring transmission of the disorder. Older studies of reproduction rates showed decreased reproduction rates in schizophrenic patients, but these rates appear to have increased over time, perhaps in part due to communitisation and lack of contraceptive advice. Also, atypical antipsychotics are less likely to induce hyperprolactinaemia and are associated with improved social functioning, thereby increasing the probability of conceiving. Assortive mating is relatively common among the mentally ill. Clinicians will see pregnancies where at least one of the parents has schizophrenia.

About 1-3% of birth defects result from drug exposure in utero. The classic teratogenic period occurs during weeks 3 to 8 post-conception, during organogenesis. Before 3 weeks, drugs may have an all-or-none effect: survival or death⁸¹⁴. After 9 weeks drugs can affect growth or functional development. Apart from huge molecules, most drugs cross the placenta. Drug efficacy may be altered in pregnancy, e.g. increased metabolism or excretion necessitating increased dosage. Perhaps 50% of pregnancies are unplanned. At least one third of pregnant women in the UK are prescribed one course of drug treatment, and 50% of pregnant women prescribed medication do not take it⁸¹⁵. We have no large clinical trials to guide our prescribing habits during pregnancy. Such studies that are available are retrospective involving, for example, chart reviews or prescription monitoring.

Dosing requirements of antidepressants increase by a factor of about 1.6 times the non-pregnant dose during the second trimester of pregnancy. (Abel, 2007, p. 641)

The long-term consequences of being born preterm *per se* should be borne in mind when interpreting the literature. A Norwegian study (Moster ea, 2008) followed up survivors of preterm birth to adulthood.

Cerebral palsy affected 0.1% of term babies v 9.1% of those born at 23-27 weeks gestation; the prevalence of intellectual disability was 0.4% v 4.4%; and the prevalence of receiving a disability pension was 1.7% v 10.6%. Gestational age at birth among those lacking medical disabilities was associated education level,

⁸⁰⁸ About 12,000 children with limb deformities due to thalidomide were born. (Tuffs, 2007b) Major limb malformations affected about a third of exposed cases. (Paton, 2008)

⁸⁰⁹ DES is unlikely to cause later psychiatric disorders according to Verdoux ea. (2007)

⁸¹⁰ Lenalidomide, an analogue of thalidomide that should also be avoided in women of child-bearing age, has been used to treat early myelodysplasia with deleted chromosome 5q.

⁸¹¹ Thalidomide was found to reduce pain in leprosy in 1964. (Bynum ea, 2006, p. 396) Adverse effects include sedation, constipation and peripheral neuropathy. Thalidomide was used for type II lepra reaction (erythema nodosum leprosum) but the WHO no longer recommends its use because of associated teratogenicity.

⁸¹² Thalidomide has immunomodulatory actions and anti-angiogenic effects against blood vessels in neoplasms.

⁸¹³ Substance abuse plus mental disorder.

⁸¹⁴ Utero-placental circulation is not established for about a fortnight and home pregnancy tests can detect pregnancy as early as day 10. This raises the problem of sudden cessation of medication with attendant risks of abstinence symptoms and relapse of the syndrome being treated. Changing from one drug (e.g. valproate) to another should preferably be done slowly (with overlap) before conception but this may be impractical and ineffective after pregnancy is discovered. (Tomson, 2009)

⁸¹⁵ According to Daughters ea (2007, p. 224), women (compared to men) less often abuse substances and start such abuse relatively late but quickly become dependent and suffer severe and early consequences and have more co-morbid psychiatric problems (anxiety and mood); they are more likely to have a substance-abusing partner and tend to cope with relationship loss by resorting to drugs; they are less likely to enter treatment because, e.g. social attitudes and responsibilities for children.

income, receipt of social security payments, and establishing a family, but not with not having a job or being involved in criminal activity.

Benzodiazepines (BZDs), diazepam in particular, are widely prescribed during pregnancy. If a tranquilizer or hypnotic is considered necessary in pregnancy or in the puerperium, then only a BZD should be used. Earlier studies suggested that the latter could cause lip, palatal, and cardiac defects but these have not been upheld. At most there is a 0.7% risk for cleft palate with first trimester exposure. One meta-analysis of cohort trials found no evidence for a connection between BZDs and teratogenesis. Unsurprisingly, since BZDs and barbiturates cause drug dependence in the unborn, withdrawal symptoms have been described in infants. Large doses can cause drowsy, floppy babies with hypotonia, respiratory problems, suckling difficulties, agitation, and hypothermia. High-dose abuse throughout pregnancy has been associated with foetal alcohol-like syndrome⁸¹⁶, but confounding by alcohol abuse is a factor to consider. (Steiner & Yonkers, 1998, p. 41) Benzodiazepines enter both the foetus and the mother's milk. Nevertheless, some authors stress the teratogenicity of BZDs and suggest that they do not be used at all during pregnancy. (Kohen, 2004) The most important time to avoid such drugs is during the first trimester⁸¹⁷. Breastfeeding may diminish BZD (or antidepressants) withdrawal symptoms in neonates exposed to these drugs during pregnancy and suddenly stopping breastfeeding or a drug by the mother may lead to an abstinence syndrome. The wisdom of stopping BZDs at the time of parturition is questioned by Wang ea (2008, p. 421) who point out that anxiety disorders may be exacerbated and that clonazepam (0.5-3.5 mg/day) has been used in panic disorder patients without ill effects in the perinatal period.

Beta-blockers have been associated with initial growth retardation, the baby catching up after birth. *Antipsychotic drugs*: There have been a few reports of neonatal Parkinsonism when the mother had been on oral or depot neuroleptics. The newborn may develop dystonic reactions⁸¹⁸, tremors, be flat and slow to suckle, jaundice, and have a low Apgar score⁸¹⁹. Very little neuroleptic actually enters breast milk: in one report (Gardiner ea, 2003) breast-fed infants were exposed to a calculated olanzapine dose of about only 1%. The neonatal mortality of the offspring of schizophrenic mothers is increased. Generally, high potency typical agents are safe and low potency typicals may be associated with a small excess of congenital malformations, although this is disputed. Howland & Thase(2002) consider typical antipsychotic drugs to be generally safe during pregnancy. Clozapine has not yet been associated with such anomalies, and there is as yet insufficient information on risperidone and olanzapine. A report by Koren ea,(2002) however, raises the possibility of neural tube defects in the offspring of obese patients with low folate levels treated with atypical agents during pregnancy. Newport ea (2007) looked at antipsychotic use close to delivery and found that placental passage ratio was highest for olanzapine, followed by haloperidol, risperidone, and (lowest) quetiapine; there were tendencies toward higher rates of low birth weight and neonatal ICU admission among neonates exposed to olanzapine. McKenna ea (2005) found that babies exposed to the newer antipsychotic in the womb were lighter than controls despite the mothers of the former having higher BMIs! However, Newham ea (2008) found that in utero exposure to atypical antipsychotics was associated with increased infant birth weight and size in relation to gestational age. But, these workers found that exposure to typical antipsychotics was associated with lower birth weight and gestational age-related size compared to a reference group! There has been concern about the anti-emetic agent prochlorperazine (Stemetil) being teratogenic when the foetus is exposed between weeks 6 to 10 of gestation. Kohen (2004)



⁸¹⁶ Foetal alcohol syndrome.

⁸¹⁷ The palate is formed during gestational weeks 5 to 9.

⁸¹⁸ Sometimes misdiagnosed as seizures.

⁸¹⁹ After Virginia Apgar, anaesthesiologist, 1953: items with what scores 2 in brackets: colour (pink overall), heart rate (> 100), respiration (strong cry), reflex irritability (cry), and muscle tone (active baby); record score of 0 to 10 (0, 1, and 2 for each item) at 1 and 5 minutes after birth; healthy baby scores at least 7 at 1 minute and 9/10 at 5 minutes. The predictiveness of the Apgar has been criticised. (Hegarty & Craig, 2007) **APGAR**: Activity, Pulse, Grimace, Appearance, and Respiration.

suggests changing from atypical to typical (conventional) drugs prior to conception. Clozapine could improve the chances of becoming pregnant by not increasing prolactin levels.

Antipsychotic drugs can cause breast engorgement and galactorrhoea⁸²⁰ and may be a factor in amenorrhoea (emotional problems are another contributor). These, together with a false pregnancy test (due to antipsychotics) may simulate pregnancy.

Tricyclic antidepressants (TCAs): According to some workers, in utero exposure to TCAs or fluoxetine (an SSRI) does not affect later global IQ, language development, or behavioural development in preschool and early-school children, or cause congenital anomalies. (Nulman ea, 2002; Simon ea, 2002; *vide infra*) Depression in the mother has a more profound effect on these parameters. A withdrawal reaction consisting of irritability, apparent abdominal cramps, restlessness, insomnia and fever, has been reported in some neonates born to mothers who received TCAs during the last month of pregnancy; constipation, tachycardia and urinary retention represent anticholinergic adverse effects; lethargy and hypotonia has also been reported. TCAs remain the antidepressants of first choice in pregnancy and during breast-feeding. Plasma TCA levels may fall (up to 65%) as pregnancy advances, perhaps as a result of an increased volume of distribution; increased dosages may be required later in pregnancy (Steiner & Yonkers, 1998, p. 40) in order to prevent relapse. Non-sedating TCAs, such as nortriptyline (Weissman ea, 2004) and imipramine, are preferred for nursing mothers: these two drugs are also less likely to cause hypotension and anticholinergic effects. Although follow up of infants whose mothers breast fed whilst on dothiepin found no problems, dothiepin has been associated with tachycardia. Also, nortriptyline may cause urinary retention in the newborn. Doxepin (not available after November, 2006), passed in mother's milk, can cause marked neonatal sedation and respiratory depression. TCAs can be given as a single nocturnal dose after the last feed – and night feeds should be avoided if possible.

Specific (or selective) serotonin reuptake inhibitors (SSRIs) should be considered in a woman prone to overdosing or who cannot tolerate TCAs. SSRIs have been associated with neonatal withdrawal phenomena: convulsions, irritability, jitteriness, tremor, insomnia, abnormal cry, and poor adaptation. Laine ea (2003) describe serotonergic symptoms⁸²¹ in newborns where the baby had been exposed to SSRIs during late pregnancy; symptoms were more pronounced if the umbilical venous 5-HIAA concentration was low. Levinson-Castiel ea (2006) found that of 60 neonates exposed who were exposed to SSRIs *in utero*, 8 had a severe and 10 had a mild abstinence syndrome. Chambers ea (2006) reported an increase in the rate of persistent pulmonary hypertension of the newborn⁸²² from 1 in 500 live births to 1 in 100. While this requires further validation, (Mills, 2006) Suri ea (2007), in a naturalistic and prospective study with pregnant women mostly treated with SSRIs and many of whom continued to have depressive symptoms, found an association between treatment and 'lower gestational age at birth and an increased risk of preterm birth', and that depressive symptoms were not associated with this risk. Oberlander ea (2006) reported an excess of low birth weight and respiratory distress in neonates born to depressed mothers who had been given SSRIs. Oberlander ea (2008), after controlling for maternal factors and dose, used population health data and found that neonatal outcome was no different between infants exposed early or late *in utero* to an SSRI but that longer prenatal exposure was associated with lower birth weight, respiratory distress and reduced gestational age ($p < 0.05$). Stopping SSRIs during the last 14 days of pregnancy seemed initially to reduce the risk of neonatal respiratory distress but this relationship was nullified by controlling for maternal (illness severity) and neonatal confounders. (Warburton ea, 2010) Some authorities avoid SSRIs during breast-feeding because "20-25%" of the maternal serum fluoxetine level is found in her milk. This can lead to neonatal agitation, insomnia, tremor, nausea, diarrhoea, rash and, rarely, convulsions. Similar effects have been reported with sertraline (although mean umbilical cord/maternal serum ratios may be lower for sertraline than for fluoxetine: Hendrick ea, 2003; Weissman ea, 2004). Other authorities say that the infant only gets 10% equivalence of the maternal dose of fluoxetine, that sertraline is undetectable in breast milk, and that SSRIs are safe. (Ericson ea, 1999) If they are really needed and the baby is healthy and carefully monitored, they are probably an option. One review of controlled prospective trials of fluoxetine in pregnancy, which looked at the IQs of offspring, were against a teratogenic effect; also, the small numbers

⁸²⁰ In both sexes – disturbed oestrogen to androgen ratio during chronic antipsychotic treatment may be more important than prolactin in male gynaecomastia.

⁸²¹ Myoclonus, restlessness, tremor, shivering, hyperreflexia, incoordination, rigidity.

⁸²² **Persistent pulmonary hypertension of the newborn** (neonatal circulation fails to adapt completely to extrauterine breathing) has been associated with SSRI exposure after the 20th gestational week.

of babies involved in short-term studies where the breast-feeding mother was on fluoxetine are reassuring. Paroxetine may be relatively safe during breast-feeding because the dose received by the baby is so low. In one overview, paroxetine in animals was not teratogenic.⁸²³ However, the FDA issued a warning in December 2005 that paroxetine use during the first trimester may increase the risk of birth defects relative to other SSRIs or no use of antidepressants, especially cardiac defects. GlaxoSmithKline issued a communiqué in May 2006 to the effect that paroxetine use during the first trimester of pregnancy is associated in some epidemiological studies with a small increase in cardiovascular malformations⁸²⁴. GSK was sued successfully in the US over claims that paroxetine caused birth defects.(Tanne, 2009b,c) The Irish Medicines Board, (2006) whilst acknowledging contradictory findings of congenital malformations, issued a warning that paroxetine only be used in pregnancy if 'strictly indicated' and that women planning a pregnancy or becoming pregnant during therapy be asked to consult their physician. However, Einarson ea (2008) found no evidence to suggest that paroxetine in early pregnancy causes cardiovascular malformations. One database analysis (Sanz ea, 2005) found that of 93 suspected cases of SSRI-induced withdrawal syndrome 64 were associated with paroxetine (fluoxetine 14, sertraline 9, citalopram 7). A prospective American study found no teratogenic effects for fluvoxamine, paroxetine or sertraline. Because of its metabolite norfluoxetine's long half-life, fluoxetine's effects may persist for many weeks despite its being discontinued, during which time the woman may have conceived. According to Nulman ea,(2002) in utero exposure to fluoxetine does not affect later temperament, language development, or behavioural development in preschool and early-school children. Simon ea (2002) reported earlier delivery and (therefore) lower birth weight in babies exposed to SSRIs in utero; third trimester exposure was associated with reduced Apgar scores. According to Austin, 2006) most neonatal adverse effects of SSRI following intrauterine exposure are 'mild and self-limiting'. First trimester exposure to sertraline was significantly associated with omphalocele and septal defects in one study, but any defects found in this study of SSRI use 'are rare and the absolute risks are small'.(Louik ea, 2007) A Danish study (Pedersen ea, 2009) found an increased prevalence of septal cardiac defects in offspring of mothers prescribed an SSRI (especially sertraline, citalopram, or more than one SSRI) in early pregnancy. Whilst stating that absolute risks are small, Alwan ea (2007) found increased risks for anencephaly, craniosynostosis, and omphalocele in cases exposed to SSRIs in early pregnancy, but they failed to find an increase in heart defects. Wisner ea (2009) found that infants exposed to SSRIs throughout pregnancy were at increased risk for preterm birth relative to those who were partially exposed and those not exposed; neither SSRI nor depression exposure increased risk for minor physical anomalies or reduced maternal weight gain; mean infant birth weights were equivalent; and the authors concluded that both continuous SSRI exposure and continuous untreated depression were associated with preterm birth rates exceeding 20%. A meta-analysis ordered by the Pharmacovigilance Working Party of the European Medicines Agency concluded that the risk of bearing an infant with a cardiovascular defect following first trimester fluoxetine exposure is about double the base rate (from 1 up to 2/100), the Agency stating that this 'small' increase must be weighed against the risks associated with not treating depression.(Anonymous, 2010a) Because of inconsistent results and methodological issues (Greene, 2007; Chambers, 2009) these studies raise the question of the ability of statistics to detect true rare associations. Risks, if present are small relative to the risk of no or inadequate treatment.(Chambers, 2009)

Monoamine oxidase inhibitors (MAOIs): Where possible, MAOIs should be avoided in pregnant women. Tranylcypromine may be relatively safe for nursing mothers but more studies need to be done in this area with the MAOIs. In general, it is safer to avoid these drugs in nursing mothers because of the risk of inducing hypertension in the infant. Some authorities view MAOIs as teratogens. An increased rate of congenital anomalies has been noted in animal studies. They can also precipitate hypertensive crises. The long half-life of tranylcypromine has similar implication as with fluoxetine above. Moclobemide appears in very low concentrations in breast milk. Caution is required where labour is concerned since MAOIs may

⁸²³ Owens(2004, p. 282) states that intradermal bruising may occur in animals exposed *in utero*.

⁸²⁴ E.g. VSD and, to a lesser extent, ASD. The risk is increased from about 1/100 to < 2/100. See also Dobson (2006) and Donnelly and Paton.(2007) In 2010 Irish and UK authorities advised that fluoxetine may be ('possible') associated with 'a small increased risk of congenital cardiac defects' when used in early pregnancy. This was accompanied by the usual advice to perform a risk/benefit analysis.

interact adversely with narcotic analgesics. They may also interact with drugs used to delay premature labour.⁸²⁵

Novel antidepressants: Much less is known about these agents, e.g. nefazodone⁸²⁶. However, venlafaxine caused no increase in the risk of major congenital anomalies in one prospective study involving 150 pregnant women.(Einarson ea, 2001)

Lithium is teratogenic during the first trimester, although the risk is small.

Lithium: risk of major congenital anomalies (Marangell ea 2003b p. 1106)

With lithium exposure = 4-12%

Without = 2-4%

Defects of the tricuspid valve⁸²⁷ are well described. Oligo- (fetal nephrotoxicity) or poly-hydramnios (fetal diabetes insipidus) may occur. Cohen ea (1994) suggest offering fetal echocardiography and high-resolution ultrasound examination at 16 to 18 weeks gestation. A fetal goiter may press on the trachea during delivery. Lithium clearance doubles during pregnancy and it may be necessary to raise the dose during the second and third trimesters in order to maintain the same serum concentration. At the time of parturition the clearance falls back to 'normal'. This may happen very quickly and the level of lithium may rise in the serum to toxic concentrations unless the dose is rapidly reduced. The ratio of lithium concentrations in umbilical cord blood to maternal blood was uniform across a wide range of maternal concentrations (0.2-2.6 mEq/L) at delivery in a study by Newport ea (2005); higher levels were associated with lower Apgar scores, longer hospital stays, and higher rates of CNS and neuromuscular complications in the newborn. Certain guidelines can be offered: stop lithium slowly before a planned pregnancy; do not give it during the first trimester; also stop it slowly before parturition or scheduled cesarean section (to avoid a cold, blue, floppy baby) or continue lithium at this time (because of high relapse risk – opinions differ); keep the serum levels just above 0.5 mmol/L during pregnancy. Fluids (IV) should be maintained during labour. Start lithium again after a few weeks if the mother agrees not to breast-feed.⁸²⁸ Some authors restart lithium as soon as mother is stable. There may be an association between lithium and premature delivery. Lithium prophylaxis in non-breastfeeding puerperal women who have a history of bipolar disorder or puerperal psychosis should be considered. Lithium enters breast milk freely (it is free in plasma, not protein bound like phenothiazines or TCAs) and so is best-avoided in nursing mothers; the possibility of lithium accumulation in developing bone is an important consideration.

Anticonvulsants & other 'mood stabilizers' are teratogenic in less than 10% of exposed fetuses. Many studies have not controlled for confounding factors such as smoking.(APA, 2009, p. 43) Stopping mood stabilizers, particularly abruptly, during pregnancy carries a high risk of recurrence of bipolar disorder.⁸²⁹ (Viguera ea, 2007) The safest anti-epileptic in pregnancy is the one that best controls the epilepsy⁸³⁰. Monotherapy is safer than polytherapy, especially if one of the drugs is valproate.(Morrow ea, 2006) If an anticonvulsant is needed then best practice dictates the co-prescription of folic acid (5 mg/day) starting before conception to prevent neural tube defects.(Anonymous, 2005b; Burt & Hendrick, 2005, p. 53; Tomson & Hiilesmaa, 2007; Clarke, 2009, p. 1143) The genotype of the exposed conceptus may be relevant in determining susceptibility to malformations due to anticonvulsants since a susceptibility gene for valproate-induced anomalies in the mouse has been located. The metabolism of most anticonvulsant drugs is increased during pregnancy.(Leonard, 2003, p. 318) A fetal hydantoin (phenytoin) syndrome has been described which consists of some degree of intellectual disability, hypertelorism, a flattened nose, epicanthic folds, low set ears, and a wide mouth. Neonatal haemorrhage has been reported in the offspring

⁸²⁵ Tocolytic agents (delay labour), e.g. terbutaline.

⁸²⁶ Withdrawn from market.

⁸²⁷ Ebstein's anomaly [tricuspid valve displaced into right ventricle]: risk = 1:20,000 of general population, and 1:700 among infants of mothers taking lithium in first trimester of pregnancy.

⁸²⁸ However, Viguera ea (2007) studied 10 mother-infant pairs and found no adverse effects of lithium on nursing infants.

⁸²⁹ Predictors of recurrence were bipolar II disorder, earlier onset, more frequent recurrences, recent illness, antidepressant use, and use of anticonvulsants versus lithium.(Viguera ea, 2007)

⁸³⁰ Epilepsy appears to be associated with diminished fertility. Menstrual disorders (due to the disease or the medication) and polycystic ovaries (caused by epilepsy or medication) play a role. Involvement of circuits between the temporal lobe and the hypothalamus may be involved. Obesity, and associated metabolic issues, may be caused by anti-epileptic drugs, particularly valproate. Anti-epileptic drugs, on the other hand, may reduce the efficacy of oral contraceptives.

of phenytoin-treated pregnant women; a similar risk applies to carbamazepine-treated cases and to prevent neonatal haemorrhage the mother should receive vitamin K 10-20 mg/day orally from the 36th week of pregnancy and the neonate should be given 1 mg intramuscularly. In fact, antiepileptic drugs in general may increase the likelihood of fetal bleeding, so vitamin K1 should be given to the mother during the last weeks of pregnancy and to the newborn in all such cases⁸³¹. Carbamazepine (which, like the antipsychotic drugs, can cause a false positive pregnancy test) given during the first trimester is associated with a 0.5-1.0% risk for spina bifida; there is also evidence for developmental delay, cranio-facial anomalies, fingernail hypoplasia, cardiovascular and urinary tract defects, hypoglycaemia, hepatic dysfunction, and, possibly, adverse effects on cognitive function. Carbamazepine may be safer than valproate. (Tomson, 2009) Oxcarbazepine⁸³², the 10-keto analogue of carbamazepine, is of unknown effect in pregnancy, although it may also be associated with facial dystrophism.

Valproic acid/valproate taken during the first trimester carries a 1-6% risk of spina bifida. The risk of major congenital malformations is 2 to 4 times higher with valproate (absolute rates 6-11%) compared to carbamazepine or lamotrigine. (Tomson et al, 2009) There is also possibly developmental delay, cranio-facial anomalies, fingernail hypoplasia, heart defects, hypoglycaemia, hepatic dysfunction, and, probably (subject to methodological issues such as non-randomised samples), cognitive dysfunction (lower IQ in offspring compared to other anticonvulsants: Meador et al, 2009). The risks of continuing valproate or carbamazepine during gestation must be carefully balanced against the chances of relapse. (Marangell et al, 2003b p. 1110 & 1112) Teratogenesis due to valproate occurs between weeks 4 and 5 (the patient may be unaware of gestational status) and this may be important in deciding whether to continue prescribing it or not. (Wang et al, 2008, p. 419) In general, avoid valproate unless it is the only drug that controls seizures in pregnancy. NICE recommends that valproate should not be routinely used in women capable of becoming pregnant.

Verapamil may be safe but its efficacy in bipolar affective disorder is not yet clear. Gabapentin, topiramate, felbamate and vigabatrin are too new to give clear guidance on, so are best avoided. Burt & Hendrick (2005, p. 54) state that lamotrigine may be safer in pregnancy than lithium, carbamazepine, or valproate, although there is evidence for a possible increase in non-syndromic oral clefts⁸³³ in the offspring of lamotrigine-treated women. (Holmes et al, 2006; GlaxoSmithKline memorandum, June 2006)

Anticholinergic agents: Trihexyphenidyl and bethanechol have been reported to be associated with minor congenital anomalies and neonatal anticholinergic effects, and amantadine is associated with cardiovascular malformations in animals. These agents should be avoided during pregnancy. Babies being breast-fed may develop dry mouth, urinary retention, constipation, and other predictable side effects. Changing an antipsychotic to a low potency agent might obviate the need for such drugs.

Methadone: It has been suggested that pregnant women should only be detoxified from opioids between weeks 14 and 32; before that there is a risk of abortion; later there is the problem of abstinence-induced fetal distress. According to Mack et al (2003, p. 367) there is no absolute contraindication to methadone during pregnancy because 'treatment of neonates for methadone withdrawal is a common procedure'. Bell and Harvey-Dodds (2008) that methadone should be continued during pregnancy. Buprenorphine may be a safe alternative to methadone in pregnancy (Fischer et al, 2006; Bell & Harvey-Dodds, 2008) and is increasingly used in such circumstances.

Codeine: This usually enters breast milk in very small amounts but mothers who are ultra-rapid metabolisers may convert much of this to morphine, with potential lethal effects for the infant.

Electroconvulsive therapy (ECT): If depression, or mania, fails to respond to drug treatment, ECT may be used without harming the fetus. (Nelson & Holmes, 1989; Miller, 1994) However, it is rarely indicated at this time. Its main indication is for severe, drug-refractory depression. The right hip should be elevated to maintain placental perfusion. Succinylcholine and glycopyrrolate⁸³⁴ appear to be relatively safe during pregnancy. (Burt & Hendrick, 2003, p. 1519) Atropine, which crosses the placenta much more efficiently than glycopyrrolate, should be avoided because it causes fetal tachycardia, variable heart rate, and may mask fetal distress. Sodium citrate may be used to reduce the risk of gastric regurgitation. (Burt & Hendrick, 2005, p. 56)

⁸³¹ These drugs cause a decrease in vitamin K-dependent clotting factors in foetal blood.

⁸³² Compared to carbamazepine oxcarbazepine has an extra oxygen atom.

⁸³³ The risk of oral clefts is about 9/1,000 births.

⁸³⁴ Glycopyrronium bromide.

Cigarette smoking: More women worldwide are smoking than ever before. Smoking during pregnancy, considered here by way of contrast with prescribed drugs, is associated with reduced placental blood flow, decreased fetal activity and breathing movements, premature delivery, increased perinatal mortality (including cot deaths: if the father, mother, or both parents smoke, the risk is increased by 2, 4, and 5 times respectively), spontaneous abortion, placenta praevia and placental abruption, histological changes in the placenta, low Apgar scores, low birth weight⁸³⁵, neonatal acidosis, urinary tract infection in infancy, atopy in childhood, higher blood pressure at 9 years and 18 years of age, and long-term negative effects on stature and educational achievement, including conduct disorder⁸³⁶, attention deficit hyperactivity disorder,(Linnet ea, 2003; Gray ea, 2009), substance abuse, violence and criminal arrest.⁸³⁷ Passive maternal smoking may affect birth weight. There is some evidence that exposure to smoking *in utero* may increase the risk of both diabetes mellitus and obesity (Montgomery & Ekblom, 2002) and the offspring may be more likely to smoke themselves as adults.(Buka ea, 2003) The risk of sudden infant death syndrome is significantly increased by exposure to tobacco smoke either during gestation or postpartum.(McDonnell ea, 2002; Webb ea, 2010)⁸³⁸ Whilst genes may account for most of the risk in offspring for developing ADHD, smoking in pregnancy may contribute to this risk.(Thapar ea, 2003) Mothers who smoke during pregnancy may have adolescent offspring who are at increased risk of experiencing psychotic symptoms.(Zammit ea, 2009) Chromosomal instability in cells recovered during amniocentesis has been reported in the case of women smoking at least 10 cigarettes daily.(de la Chica ea, 2005) Exposure to maternal smoking *in utero* was found to be associated with detectable changes in DNA methylation patterns of their children (epigenesis) both globally and in the promoter region of genes involved in cancer or development.(Breton ea, 2009) Simple interventions, such as self-help booklets, are unlikely to stop pregnant women smoking.(Moore ea, 2002) Nicotine replacement therapy, whilst best avoided in pregnancy and during breast-feeding, is probably safer than smoking.(Molyneux, 2004; Coleman ea, 2004) Smokeless tobacco (marketed as a relatively safe form of tobacco) use during pregnancy reduces birth weight and increases the likelihood of preterm delivery.(Prakash & Streevidya, 2004) Stopping smoking before the 15th week of pregnancy seems to reduce the rates of spontaneous preterm birth and small for gestational age infants to those of non-smoking mothers.(McCowan ea, 2009)

Caffeine: Caffeine is the most common xenobiotic⁸³⁹ consumed during pregnancy. Maternal caffeine intake is negatively correlated with birth weight if the mother already smokes. Excess caffeine is best avoided because it may be associated with restricted fetal growth (CARE Study Group, 2008) and an increase in the stillbirth rate.(Wisborg ea, 2003)

*Fetal alcohol syndrome (FAS)*⁸⁴⁰ can include various combinations and degrees of severity of stigmata. Apoptotic neurodegeneration follows alcohol-induced NMDA receptor blockade and GABA receptor activation.(Hotchkiss ea, 2009)

Stigmata of FAS

Antenatal growth retardation

Microcephaly, porencephaly, agenesis of corpus callosum, spinal dysraphism

Prominent forehead

Maxillary hypoplasia, cleft palate

Microphthalmia/epicanthal folds, short palpebral fissures

Long (or smooth) philtrum with corresponding reduction in vermilion of upper lip

⁸³⁵ The effect of smoking on birth weight may depend to some degree on maternal genotype, e.g. the Aa or aa genotype for CYP1A1 may carry over 3 times the risk associated with the AA genotype.

⁸³⁶ The relationship is heavily confounded by other known risks.(Maughan ea, 2004)

⁸³⁷ The last findings may be mediated via substance abuse in the offspring[Brennan ea, 2002], although other factors, such as delivery complications and unwanted pregnancy, may play a part.(Ishikawa & Raine, 2003, p. 666) Lotfipour ea (2009) found that prenatal exposure to maternal cigarette smoking was associated with increased likelihood of substance use and that exposed adolescents with thinning of the orbitofrontal cortex (OFC) were more likely to experiment with drugs but that non-exposed adolescents were more likely to have a thicker OFC the more drugs they had tried, the latter effect being modified by a BDNF genotype (Val66Met).

⁸³⁸ Of course, there are other known risk factors for SIDS, such as co-sleeping.(Mitchell, 2009) Parental mental illness, including alcoholism, appear to be important contributors to SIDS.(Webb ea, 2010)

⁸³⁹ A chemical found in an organism that is not normally produced or expected to be present in it, e.g. antibiotics.

⁸⁴⁰ Described in 1973. In *State vs Deborah Z* a mother who drank during pregnancy was not held responsible for FAS because the Wisconsin Appeals Court stated in 1999 that a fetus is not legally a human being. A similar situation applies in the UK.(Mukherjee ea, 2007)

Short upturned nose
 'Railroad track' ears
 Cardiac septal defects
 Pectus excavatum
 Fine motor dysfunction, developmental delay or intellectual disability

The alcohol levels of the mothers whose offspring had these signs were, it must be stressed, very high. There is evidence for an increase in spontaneous fetal loss, but whether this excess occurs in the first or second trimester is not yet clear. Alcohol-related late abortions and premature deliveries are much more noticeable among heavy drinkers. Joy ea (2003, p. 566) take a very broad view of fetal alcohol exposure effects, warning clinicians of the need to consider them even when a patient's appearance is unremarkable, and they suggest such exposure 'may be the single most frequent cause of' intellectual disability, 'at least in the developed western world'. They put the incidence of FAS as 1/2,000-3,500 live births, and 'far more frequently' in groups such as Native Americans. One group found no correlation between the mental and physical development of 18-month-old children and their mother's weekly consumption of alcohol at levels in excess of 100g of absolute alcohol. In a 10-year follow up of 60 FAS cases, others noted that cranio-facial malformations diminished over time, but microcephaly, and to a lesser extent short stature, persisted. Boys remained underweight, but body weight normalized in girls during adolescence. Mental handicap persisted and was little influenced by environmental or educational interventions. Follow up of FAS adults over 18 years of age with an IQ in excess of 70 has revealed a high incidence of alcohol (supported by Baer ea, 2003: prenatal exposure to alcohol is a risk factor for problem drinking at 21 years of age) and substance dependence, depression, psychosis⁸⁴¹, and avoidant and antisocial personality disorders. Cigarettes cause less damage to the foetus than does alcohol when either is taken in average amounts. Alcohol causes greater damage when large quantities are taken. Moderate drinking, arbitrarily defined as one alcoholic drink per week to 1.5 drinks per day, and occasional or non-drinking seem to affect the foetus similarly. Binge drinking during pregnancy was associated with an excess of substance dependence/abuse and passive-aggressive/antisocial traits/personality disorders in offspring examined at a mean of 25.7 years.(Barr ea, 2006) Most babies born to heavy drinkers, including alcoholics, are normal. Mothers who take an occasional drink during pregnancy may have little to fear, although Mukherjee ea (2005; 2007) and the BMA (Hitchen, 2007) counsel complete abstinence⁸⁴². Disulfiram use during pregnancy has been associated with fetal limb deformities. Too little is known about acamprosate in pregnancy.

Discussion: 1-2% of pregnancies in developed countries may be associated with some form of foetal abnormality. Before prescribing, a risk-benefit analysis is mandatory, as is full discussion with the patient and her partner. Women on antidepressants should receive counselling before conception⁸⁴³ and, where feasible, tapering and stopping of the drug before trying to get pregnant; they should also have been in receipt of counselling about how to prevent conception in the first place. *In general, older drugs are preferable to new ones.* Most antihistamines are considered safe in the short term, although diphenhydramine has been associated with cardiovascular malformations. The analgesic of choice is paracetamol⁸⁴⁴. Avoid preparations containing alcohol, NSAIDs and iodine, e.g. as found in cold and cough cures. In cases of insomnia, sleep hygiene measures (e.g. regular times for retiring and rising, including weekends and holidays, and exercising during the day but not shortly before sleep), stimulus control (retire only when sleepy, get up for a period if unable to sleep and return to bed when drowsy), sleep restriction (adjust time in bed depending on how much of it is spent in sleep), paradoxical intention (deliberately trying to stay awake reduces performance anxiety and increases likelihood of sleep), cognitive therapy, muscle biofeedback, and relaxation exercises should be tried first.(Sateia & Nowell, 2004) Anything else that can be treated is treated next, e.g. itch or pain. Avoid hypnotics if possible. Late third trimester BZD use is of greatest concern because of floppy infants and neonatal withdrawals. Chloral hydrate is a pro-drug that needs to be metabolised to trichlorethanol to produce an hypnotic effect. It has a

⁸⁴¹ Zammit ea (2009) found that women consuming over 21 units of alcohol/week were at risk of having adolescent offspring who experienced psychotic symptoms.

⁸⁴² This is because behavioural problems in infants have been found after their mothers drank as little 1 drink/week. See also O'Brien ea.(2007)

⁸⁴³ This includes all women of child-bearing age.

⁸⁴⁴ Acetaminophen in USA.

narrow therapeutic window (10 mgs. can cause lethal respiratory depression), potentiates the effects of alcohol, has a high abuse potential, and, on cessation, can be associated with very unpleasant withdrawal effects.(Wood, 1997) It has been used recently to sedate children undergoing MRI scanning, with no respiratory complications, when general anaesthesia was unavailable.(Low ea, 2008) The newest drugs, zopiclone (Zopitan) and zolpidem (Stilnoct), should be avoided because of unclear data, as should buspirone⁸⁴⁵.

Depression in pregnancy may respond to non-drug therapies such as environmental manipulation or cognitive therapy (if available). However, medication is often essential.(Mills, 2006) Do not prescribe unless it is essential to do so and record discussions with patient/relatives in the case notes. **Each case is decided on its own merits, keeping in mind that 10% of pregnant women meet standard diagnostic criteria for depression and that relapse rates following discontinuation of medication are high.** TCAs should be slowly tapered and stopped before delivery to avoid neonatal neuromuscular irritability, restlessness, fever and fits.

Ramos ea (2008) found no support for a connection between duration of antidepressant use in general during the first trimester of pregnancy and major congenital malformations diagnosed during the first year of life. It is probably safest to avoid breast-feeding premature babies if the mother is on psychotropics because of hepatic and renal immaturity.

Lithium, TCA and SSRI use in pregnancy is justified *if clinically essential*. Untreated maternal illness may adversely affect obstetric outcome. The nursing infant's daily dose of drug is less than the mother's daily dose. Some authorities are more inclined to stop breast-feeding if the mother is on high doses or combinations of antidepressants⁸⁴⁶. Oestrogens, which may help some cases of postpartum depression, should not be combined with breast-feeding. Interpersonal psychotherapy,(O'Hara ea, 2000) various brief therapies, and counselling (again, depending on availability) are effective alternatives to medication for postpartum depression.

Regarding OCD, it has been suggested that clomipramine is generally safe, despite anecdotal reports of neonatal seizures at time of labour/delivery. SSRIs are *probably* also (relatively) safe. Expert use of exposure and response prevention are alternatives to drugs.

It should be recalled that schizophrenia itself appears to be associated with minor physical anomalies.

Some tentative conclusions derived from a review of the salient literature are shown in the box.

Nevertheless, manufacturer's guidelines should be consulted before prescribing.

Some conclusions

Interpreting statistics: Clinicians and their patients are bombarded with novel drug-risk information.(Avorn & Schneeweiss, 2009) When data on numerous patients taking many compounds are analysed it is inevitable that statistical significance will emerge, sometimes by chance alone. P-value-based thresholds may not tell us anything about severity of the alleged adverse event and fail to provide guidance on safer treatments or factor in benefit from the indicted compound. Hasty reactions may lead to discontinuation of efficacious interventions whereas non-reaction might lead to 'another thalidomide'!

Pregnancy: Polypharmacy is best avoided and doses should be as low as is compatible with maintenance of health. TCAs and fluoxetine do not seem to cause congenital malformations (CMs) and are probably relatively safe. Nevertheless, data on neonatal withdrawal syndrome suggests caution. Reports of a small risk for cardiac defects (paroxetine, fluoxetine) and persistent pulmonary hypertension of the newborn (SSRIs) require further research. Paroxetine is probably best avoided during pregnancy until matters are clarified. Authorities, including the FDA, often suggest discontinuing antidepressants prior to delivery; however, this puts the patient at risk during the high-risk postpartum period. There have been a few reports of MAOIs and associated CMs in humans, more so in animal studies, and they are usually avoided. ECT is as safe as at other times of life. Bupropion use during pregnancy does not appear to be associated with an excess of malformations.(Wang ea, 2008, p. 416) The following drugs are associated with no clear data; only small samples have been reported; and they should not be seen as first-line therapies: psychostimulants, trazodone, venlafaxine, and nefazodone (withdrawn, 2003). Lithium is safer than anticonvulsants (for mood disorders). If used, it should be avoided during the first trimester, and levels

⁸⁴⁵ Buspar was withdrawn, December 2009.

⁸⁴⁶ E.g. Fava and Papakostas (2008, p. 609) discourage mothers from breast-feeding if they are on TCAs.

should be monitored frequently with changes in dosages as necessary. For people planning a pregnancy who are receiving anticonvulsants and who have never been on lithium it may be worth considering a trial of lithium during the non-gravid period. Serum anticonvulsant levels may drop during pregnancy and so should be monitored carefully. Alcohol and nicotine intake can damage the foetus (vide supra). Multiple dosing of neuroleptics (instead of a larger once a day dose) is advised during pregnancy to avoid peak serum concentrations. General advice regarding antipsychotics is to have a drug-free interval around delivery, which necessitated changing to oral medication. The last depot injection can be given at week 28 of the pregnancy and a high potency agent is started on the date when the depot would have next been due. The dose is increased to rough equivalence with the depot and it is again reduced, starting 2 weeks before the expected date of delivery, the aim being to have the mother drug-free 2 to 3 days before onset of labour. Neuroleptics are rapidly reinstated (oral plus depot) shortly after the baby is born. Strong consideration should be given to giving folate supplementation to pregnant patients on atypical neuroleptics. First trimester exposure to folic acid antagonists⁸⁴⁷ should be avoided as far as possible since they double the risk for congenital malformations and increase the risk for neural tube defects six times. (Matok et al, 2009b) Excess coffee intake during pregnancy may be associated with an increased risk of stillbirth. (Wisborg et al, 2003) The decision to employ SSRIs is made on a case-by-case basis in consultation with mother and her significant other. (Austin, 2006)

Breast-feeding: Exposure is reduced by taking medication just after breast-feeding⁸⁴⁸ and by discarding hind milk (contains a higher concentration of milk). Premature infants (immature P450 enzymes) or those with poor liver function are least likely to be able to handle drugs transmitted via mother's milk and it is often decided to defer breast-feeding in such cases. TCAs are usually well tolerated (doxepin may be an exception). SSRIs are mostly safe. High levels of bupropion in breast milk were devoid of adverse effects but data is very limited. BZDs are well tolerated (use lowest possible dose; avoid if infant premature; observe for sedation/CNS effects). Antipsychotics have limited data but probably safe (do not breast feed if on clozapine; [Howard et al, 2004; Kohen, 2005] one case of excessive sleepiness and one case of reversible agranulocytosis in infants breast fed by clozapine treated mothers: Dev & Krupp, 1995) – the older ones have more data than the newer 'atypicals'; however, there is some data attesting to the safety of olanzapine in small numbers of offspring of breastfeeding mothers. (Cohen et al, 2004, p. 602) Malt and Lloyd (2007, p. 785) suggest that sulpiride is the antipsychotic of choice during breast-feeding because of the very low milk levels achieved. Milk lithium levels are up to half maternal plasma levels - if used observe closely, especially infant's fluid status. Valproic acid and carbamazepine (very cautious: breast milk levels are low) use require close monitoring because of the risk to the infant of liver problems and white cell toxicity, although only low levels appear in maternal milk. Adele C. Viguera of Boston (2004) recommended breast feeding to bipolar patients on mood stabilisers. Bromocriptine should be avoided as it suppresses lactation.

In cases of doubt, many clinicians advocate bottle feeding rather than leaving the mother's (serious) mental disorder untreated. It should be noted that stress in later pregnancy has been correlated with preterm delivery. Progestogens inhibit the metabolism of many psychotropic drugs: therefore, stopping a contraceptive preparation may necessitate increasing the dose of a psychotropic, and pregnant women, who have elevated progesterone levels, may need lower doses of psychotropics during gestation, their dosage requirements increasing after delivery. Interestingly, although progesterone is widely used for postnatal depression there is no evidence that it works, and postnatal norethisterone may increase the risk of depression. Oestrogens on the other hand may relieve some severe cases of postnatal depression. The latter may be tried alone or with a standard antidepressant drug.

Where available, psychotherapy may obviate the need for medication in selected cases. A morning walk or light therapy may help patients with seasonal affective disorder; and those with regular summer depressions may benefit from cooling and dark glasses.

Finally, some pregnant women use illegal drugs, e.g. urine testing of pregnant women and post-delivery mothers in Dublin (Bosio et al, 1997) found a prevalence of 2.8%, the most commonly detected drug being cannabis.

⁸⁴⁷ **Folic acid antagonists** include dihydrofolate reductase inhibitors (e.g. trimethoprim and sulfasalazine) that prevent conversion of folate to active metabolites and drugs that reduce serum/tissue folate levels (e.g. carbamazepine, phenytoin, lamotrigine, primidone, valproic acid, phenobarbital, and cholestyramine).

⁸⁴⁸ The problem here is that newborn babies usually feed every 2-3 hours.

Evidence-based medicine (EBM)

'A truth which is clearly understood can no longer be written with sincerity'. (Marcel Proust, 1871-1922)

'Thus, even if not entirely evidence based, psychiatry should always be evidence informed'. (Puri & Treasden, 2010, p. xi)

Levels of evidence in clinical research are shown in the box.

Levels of evidence

Level I DBRCT* - Ia, PC**; Ib, non-PC, meta-analysis/systematic review

Level II Open randomised trial

Level III Observational study – IIIa, non-randomised, controlled study; IIIb, large (> 100 cases) non-randomised, uncontrolled study; IIIc, medium-sized (50 to 100 cases) non-randomised, uncontrolled study

Level IV Small (10-50 cases) non-randomised, uncontrolled study

Level V Expert review/opinion***, single cases (case report) or less than 10 cases (case series)

* Double-blind randomised controlled trial. ** Placebo-controlled. *** 'Eminence-based medicine'.

Steps in evaluation of evidence (Carney, 2010, p. 17)

What am I not sure about and how can I put this in question form?

Where can I find answers, how do I go about it, and how do I measure level of evidence?

How does the available evidence apply to my patient?

Provide information to my patient in a sensitive and balanced fashion in order to elicit informed consent

Monitor performance to enhance learning

No one published research paper should be interpreted in isolation. (Glasziou et al., 2004) EBM consists of a set of strategies designed to help clinicians keep abreast of developments and to base decisions on best available external evidence. A precise definition of the clinical problem is mandatory, as are an efficient search for the best available evidence, and a critical appraisal of the evidence. Evidence must be integrated with clinical experience: EBM v PBM (practice-based medicine: Travis & Azorin, 2002; Battaglia & Ogliari, 2004; Coomarasamy & Khan, 2004) EBM users should assess the outcome of the process and continue to improve their skills in using this approach. Absence of research evidence forces one back on clinical experience. According to Geddes (1997), clinical practice lags behind research, although one can legitimately argue that much research lags behind clinical need and may not be applicable to clinical work. Also, sources of evidence vary greatly in quality (Kelly, 2002) and the message given out. (Straus & Jones, 2004) In the real world of clinical medicine, evidence from randomised controlled trials, which often disagree with one another, is insufficient on its own to inform practice, and all possible sources of information should be tapped, not least the patients themselves. (Baldwin, 1999) Depending on the published evidence one reads, for example, exercise relieves minor depression⁸⁴⁹, reduces the number of depressive symptoms but does not affect the incidence of depression, or increases the risk of becoming depressed! (Baldwin et al., 2002, p. 86) In summary, while a degree of consensus is necessary among colleagues, the ideology of EBM should not become so entrenched as to ignore clinical complexity. (Williams & Garner, 2002; Berrios & Marková, 2002; Cooper 2003; Wu, 2005) Clinicians need to acquire the skills necessary to interpret published research. (Straus, 2004) Even if the evidence exists for a particular strategy it is not always certain that it will receive funding. Every patient is unique and blind application of EBM is inappropriate and doctors should not be pilloried by the legal profession for practising their ancient art. (Hurwitz, 2004) Of course, practitioners who deviate from guidelines based on research should document their reasons for doing so. (Tallis, 2004, p. 35) Randomised control trials have uses (valid) and weaknesses (not generalisable), as has 'lower order' evidence (generalisable, if not 'valid'). (Ghaemi, 2003, p. 55) It should be recalled that Cade's original post-rodent human study of lithium therapy in mania was tiny (n = 10) and many years passed before the efficacy of lithium was 'proven'. Finally, studies can be classified into 'positive' (e.g. efficacy of a treatment is confirmed), 'negative' (e.g.

⁸⁴⁹ In animal studies, running mice show increased neurogenesis in the dentate gyrus of the hippocampal formation. (Stahl & Niculescu, 2002, p.41) Playing with dolphins may be a better antidepressant than simply playing in water (Coryell, 2008, p. 519), the so-called 'biophilia' hypothesis.

finding that a particular treatment does not work) and ‘failed’ (e.g. failing to discover what was not sought, such as an adverse effect).

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7

Psychiatry of Intellectual Disabilities

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DEFINITIONS

Many terms have been used to describe people with intellectual disability (ID) in the past, including mental handicap, mental retardation, subnormal, feeble minded, moron, idiot and imbecile. These terms have tended to attract the stigma attached to the group they describe.

The term Intellectual Disability has increasingly being used by the International Scientific Community. In Ireland, Learning Disability or ID usually means people who meet World Health Organisation (ICD-10) definition of 'Mental Retardation'. ID is a 'condition of arrested or incomplete development of the mind', characterised by a:

- Significant global impairment of intelligence.
- Significant impairment of social or adaptive functioning (which is ability of a person to effectively interact with society on all levels and care for one's self).
- That arose during the developmental period.

The *Mental Health Act (2001)* specifies three categories of 'mental disorder', one of which is 'severe intellectual disability'. This definition incorporates (approximately) the ICD-10 definition, but in addition the intellectual disability is associated with 'abnormally aggressive or seriously irresponsible conduct on the part of the person concerned'. In completing Orders under the Act (**Section 3**), doctors recommending admission need to specify the category of mental disorder requiring compulsory treatment in hospital.

The World Health Organisation in their *International Classification of Functioning Disability and Health (2001)* recognises the following components to disability:

- *Impairments* are problems of body function or structure such as significant deviation or loss.
- *Activity limitations*⁸⁵⁰ are difficulties an individual may have in executing tasks or actions.
- *Participation restrictions*⁸⁵¹ are problems an individual may experience in involvement in life situations. It is important to consider the part that society plays in restricting an individual's participation.

Intelligence can be considered the sum of those cognitive abilities that underline adaptation to the environment. Intelligence is assessed using intelligence tests, the results of which are often reported as Intelligence Quotient (IQ). In children, IQ is the ratio of mental age (MA) to chronological age (CA).

$$\left(IQ = \frac{MA}{CA} \times 100 \right)$$

Intelligence tests are standardised to have a mean IQ in the population of 100, with a standard deviation (SD) of 15. These tests attempt to be independent of culture, but cultural biases remain. Their reliability can

⁸⁵⁰ Activity limitations were known as 'disabilities' in the 1980 WHO Classification of Impairments Disabilities and Handicaps

⁸⁵¹ Participation restrictions were known as 'handicaps'

be affected by degree of co-operation, performance anxiety, and mental and physical illness. They correlate only moderately well with measures of adaptive function. For example, *WISC-III* is one of those tests. (Wechsler D, 1991)

ICD-10 subdivides people with ID into four subtypes based on severity of intellectual impairment:

Severity Intellectual Disability	Prevalence	IQ range	Clinical Picture (ICD-10)
Mild	3%* (males predominate)	50-69	Language acquisition delayed but can use speech for everyday purposes - frequent reading and writing problems Mostly independent in self care Capable of practical jobs Social and emotional immaturity may occur
Moderate	0.3%	35-49	Language acquisition slow and eventual achievement limited Support required in self care Simple practical work possible under supervision Often develop significant social skills
Severe		20-34	
Profound	0.05%	<20	Language limited to understanding simple commands/making simple requests. Often non-verbal. Multiple physical disabilities common. Poor motor skills. Often incontinent. Very little ability to care for basic needs - require constant help and supervision Can learn some new skills - but very slowly

*not all of this 3% have significant impairment of adaptive behaviour

Prevalence of more severe ID may be influenced by increased survival of premature babies, prenatal screening and selective termination, trend to later childbearing, and survival into older age of people with severe ID.

AETIOLOGY

An ID is not an illness entity in itself but the developmental consequence of some pathogenic process. Aetiology of ID may be grouped into prenatal, perinatal and postnatal, depending on the timing of the brain insult or development of pathology. The effect of the process upon the brain may have physical, cognitive and social consequences. In many of those with mild ID, and some with more severe disability, no specific syndrome can be identified to account for the disability. It is believed that in approximately 30% of people with severe ID and in 50% of those with mild ID, a cause cannot be identified.

Mild ID is known to be associated strong environmental factors such as social class (V) and other family characteristics like overcrowding, poverty, irregular unskilled employment, and intellectually "uninterested" parents. In many people with an ID, the disability accounts for by the lower end of the (near) normal distribution of intelligence. This appears to be familial, and dependent on both environmental and genetic influences.

Some specific causes of intellectual disability are:

<i>Pre-Natal (before birth)</i>	<i>Perinatal (birth-1 month of life)</i>	<i>Post-Natal</i>
<ul style="list-style-type: none"> • Chromosomal • Genetic • Metabolic • Nutritional • Infections • Drugs & alcohol • Antenatal complications • Maternal infections 	<ul style="list-style-type: none"> • Abnormalities foetal growth • Prematurity • Obstetric complications • Labour complications 	<ul style="list-style-type: none"> • Infections • Brain injury • Allergic/vaccine reactions • Accidents • Deprivation & abuse • Epilepsy

Some specific pre-natal causes of ID are summarized as follows.

Autosomal dominant conditions

- *Tuberous sclerosis* (variable disability, cafe-au-lait spots, epilepsy, brain nodules, renal and retinal lesions, genetic heterogeneity with 9 & 16 chromosomes implicated)
- *Velocardiofacial syndrome* (microdeletion at 22q11.2; congenital abnormalities of palate and heart, and a characteristic long face; associated with learning disability and a schizophreniform psychosis)

Autosomal recessive conditions (mostly inborn errors of metabolism)

- *Phenylketonuria* (ID, epilepsy, microcephaly, autistic features, eczema). 1:10,000 live births, newborn screening at 6-14 days (Guthrie test). Lack/inactivity of phenylalanine hydroxylase. Treatable if dietary phenylalanine restriction commences early.
- *Fragile X syndrome*, second most common specific cause of ID, after Down's Syndrome. 0.5-1:1000 males and 1:2000 females. Accounts for about 7% of moderate and 4% of hitherto unexplained mild ID. The fragile site is located at the long arm of the X chromosome (Xq27.3) and consists of excess CGG triplet repeats. The condition can be transmitted through non-disabled males or those who show no fragile site. Women are less severely affected than men and are usually unaffected carriers. May show *anticipation* (increased severity of disorder and earlier age of onset in progressive generations). Symptoms and signs include macro-orchidism, large ears, LD, microcephaly, marked social fears, autism, speech & language problems.

Chromosomal Abnormalities: cause 40% of severe ID; includes aneuploidy, deletions, translocations

- *Down's syndrome* is the commonest specific cause of ID, causing 30% of severe ID. 1:650-1000 live births. 94% of individuals have trisomy 21, 2% show mosaicism and 3% translocation. Increased risk of recurrence if extra chromosome due to translocation (this type is independent of maternal age). Increased risk factors include older mothers, but most infants are born to younger mothers. The syndrome is characterized by craniofacial abnormalities, cardiac defects, gastrointestinal abnormalities, hypothyroidism, acute leukaemia, depression and dementia in about 45% of those >40 yrs.

Sex Chromosome Abnormalities

- Turner's Syndrome (usually normal intelligence) - 46X0 karyotype
- Klinefelter's Syndrome (associated with mild LD) - 47XXY
- 47XYY Syndrome
- 47XXX Syndrome

Neural Tube Defects

- Incidence varies even within restricted geographical areas. Nutritional factors (folic acid) are important environmental components. May occur as part of other syndromes with severe malformations

HISTORICAL PERSPECTIVE

Caring for people with ID requires an understanding of the history of ID services. A wide number of philosophical and legislative shifts in ideology have impacted on the lives of people with ID and their carers. Changes in ideology over the years have seen perceptions move from people with ID being feared and dehumanized, to being seen as in need of care and protection, to a welcome and significant emphasis on people being seen as capable citizens with their own rights. People with ID were viewed as incapable and incompetent in their capacity for decision-making and development. Fortunately, within the last 40 years we have moved from institutional models of care, with the closure of long-stay institutions to models of care which promote social inclusion and ordinary living.

Modern Western health care provision is now primarily community-based. Modern mental health services for people with ID have either developed as part of general ID services or into specialist mental health teams. Support services are based on community inclusion, using concepts such as [social role valorization](#) and increased self-determination. But this has definitely not been the case throughout history. Here there is a brief explanatory summary of the changes that have occurred in the history of the health care and social care for people with ID.

Date (Society)	Health Care	Social Care	Education	Legal
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Medieval (Feudal)		Parish relief Living in small communities		<i>Perogativa Regis</i> to take custody of estate until death
17C-18C (Industrial revolution)	Workhouse hospitals	Poor Laws Workhouse		
19C 1900's (Empire)	Asylums Degeneracy Eugenics	Segregation Stigma	Education compulsory for most - some 'ineducable' 'defective' children segregated	<i>Elementary Education Act 1876</i> <i>Lunacy Regulation Act, 1881 (Wards of Court)</i> <i>Trial of Lunatics Act, 1883</i> <i>Idiocy Act 1886</i> <i>Education Act 1899</i>
1910s 1920s 1930s	Medical Model Responsibility Sterilisation Idiot/Mongol/ Feeble Minded Nazi 'euthanasia'	Local authority institutions Moral defectives		<i>Mental Deficiency Act 1913</i> <i>Constitution of Ireland (1937)</i>
Late 1940s (Post-war)	Custodial care Institutions Medicalisation	Transfer of care to Institutions	'ineducable' category retained	<i>Mental Treatment Act (1945)</i>
1950s 1960s	Institutional scandals (UK)	Training, Day Care, Hostels, Residential homes Report of the Commission of Inquiry on MH - 1965		
1970s	More institutional scandals Community Care Normalisation*	'Better services for the mentally handicapped' (1971) - more local authority services, hospital closures planned		Irish Health Boards established. Statutory state care for people with learning Disabilities

1980's 1990's 2000's	Discharges commence in earnest to Community Proposed development of specialist community healthcare/Mental Health teams Access to primary care	Social care needs Advocacy Small houses Integration	Special educational needs More integration with mainstream	<i>Education Act (1998); Mental Health Act (2001); Education for persons with Special Educational Needs, (2004); Criminal Law (Insanity) Act (2006); Discussion Document, Law Reform Commission (2006) 'Vulnerable Adults'</i>
	<i>Planning for the Future 1994 Discussion Document on Mental Health Needs of People with ID 1996 Strategy for Equality 1996 Quality and Fairness 2001 Review of Access to Mental Health Services (NDA), 2003 Proposed Model for the Delivery of Mental Health Services 2004 Vision for Change 2006.</i>			

*Normalisation is making available to people with ID patterns of life and conditions of everyday living as close as possible to the regular circumstances and ways of society.

EFFECTIVE COMMUNICATION

Good communication is essential in all health care settings where people are often feeling unwell, are in unfamiliar environment and are trying to understand and retain medical information. All this limits communication, comprehension and social skills. Therefore, understanding and improving communication can greatly enhance clinical care and the experience of people with ID and those working with them. Research indicates that 50% to 90% of people with ID have communication difficulties. The higher incidence of sensory, physical, visual and hearing impairments in people with ID can also impact on their communication skills. People with ID are also more likely to depend on others so therefore the importance of establishing good communication to meet their needs and wishes and to have those acted upon. Good communication will include spoken language, non-verbal communication such as facial expression, body language and gestures and any written forms of communication. Considerations should also be made to ensure that communication is culturally appropriate with increased use of interpreters versus reliance on family members.

Communication skills of people with intellectual disabilities can be divided as following:

-pre-verbal: this means that people do not have the cognitive abilities to understand words: they have profound and multiple learning difficulties; they can be helped to understand through routines, tone of voice, repetition, the context of the situation, objects and their own experience.

-non-verbal: this means that people have the ability to understand words but do not have the ability to express themselves using words and will use alternative means, such as signing or pictures.

-verbal: this means that people have a variety of skills in understanding language and expressing themselves, predominantly using speech.

As mentioned, people with an ID often find it possible to understand what is being said, even though some words are not understood as they use a variety of different strategies. These include the familiarity with the context or the person speaking, guessing or understanding of speaker's non-verbal cues such as body language, facial expression and gestures or signing. As we know non-verbal communication is very powerful and people gain around 55% of the information through body language and 38% through the tone, pitch and intonation, leaving only 7% to the actual verbal language information.

Although literacy skills are often reduced in people with ID many can understand written information when they have support such as pictures, symbols and photos. Another relevant factor that influences communication is the context. The physical environment can easily be manipulated in most circumstances and ideally this would be a quiet and comfortable environment as many people with ID have sensory hypersensitivities and this can be the cause of distress and the origin of some challenging behaviours. It is important to consider also the emotional context for the individual with ID, for whom emotional self-regulation might be largely dependent on his/her cognitive abilities, social skills and previous experiences. Some tips for good communication between health professionals and people with an ID include:

- Speak slowly; using everyday words, simple grammar and short sentences, that is plain English with no jargon.
- Use pictures/photographs to help explain or draw pictures.
- Link your explanation with everyday things especially if you need to talk about more abstract things such as time concepts.
- Write the key information down and then people can go through it with a friend/carer/support worker afterwards.
- Be aware of your facial expression and body language. Are they giving the same message as your speech? Use lots of non-verbal feedback, especially head nods and facial expression to show that you are listening.
- People with ID may have difficulties ignoring distractions. Make sure that you are talking to them in a quiet place.
- Think about how to ask questions. Remember that open questions can be more difficult. Closed questions, that are yes/no questions, are often not helpful as people may answer "yes" because they think you want them to say yes. Either/or questions may be easier, but keep them short, so that they do not just repeat the last thing you say, for example, "do you like tea or orange juice?"
- Give the person plenty of time to respond; you might have to wait longer than you expect.
- Check the person has understood you. You may need to ask them to repeat back what you said. Some people will find this hard to do.
- Be aware of other things that may affect communication, for example hearing difficulties, vision problems, physical and mental health problems, epilepsy, medication related issues, time of the day, general mood, interest in the topic.
- Be sensitive to any cultural "rules" the person may have, particularly with regard to eye contact, personal space and gestures that may have different meanings. Check what language the person is most comfortable with and whether you would need an interpreter.
- Some people with ID have more difficulties with using language in a particular manner, particularly those with autism. They might use learnt phrases or echo what is being said or what they have heard from past experiences.

HISTORY TAKING AND MENTAL STATE EXAMINATION

The format of history taking and assessing adults with intellectual disabilities is broadly similar to that used in the general population but as there are some differences these will be considered in the following section.

1. History taking

People with ID constitute a heterogeneous population ranging from non-verbal individuals with profound disabilities to those with borderline/mild disabilities and good linguistic skills. Most of the observations in this section refer to those with moderate, severe or profound ID.

The recognition of mental disorders in people with an ID is particularly difficult, due partly to linguistic limitations that often make it difficult for the individual to describe psychiatric symptoms, and partly to diagnostic overshadowing (ascribing the symptoms and signs of mental illness as being normal or due to the person's lifelong ID). In addition, people with ID who present to psychiatrists, often have baseline behaviour that would be considered abnormal in people without ID. Therefore, diagnosis depends on the interaction of a number of factors such as what the person says they are experiencing, what others say about them, how they are seen to behave and the history of their complaint.

While much of the psychiatric interview for people with ID is similar to that of other people, there are certain differences that require to be highlighted:

- Limited communication skills

As we mentioned in the previous section, many people with ID have limited communication skills, and may have difficulties in describing their symptoms. They have also difficulties understanding questions so questions should be asked in simple language, using short sentences, appropriate to the adult's developmental level. The assessment may need to be repeated, and longer periods of time may be needed for answers to be given and understood.

- Acquiescence

People with ID are more likely to acquiesce to what they believe the interviewer wants to hear. While minimizing the tendency to acquiescence is a skill that has general applicability to any psychiatric interview, it is particularly important in this population. The attitude of anyone being interviewed is likely to be influenced by expectations of the interaction. People with ID may have had negative experiences of interviews with professionals that colour their expectations. It is therefore important for the interviewer to maximise the patient's confidence and sense of security by extensive explanation of the purpose of the interview as well as constant reassurance.

- Short attention span

Persons with ID often have a short attention span. Therefore it is important to recapitulate and summarize previously stated material. This has the benefit of re-engaging and focusing the patient's attention as well as giving an opportunity to collect more detail, in addition to allowing the patient to agree or disagree with the interviewer's interpretation of what has been said.

- Linguistic and phonological problems

A wide range of linguistic and phonological problems, including poor grammar and abnormal intonation, can make patient's responses difficult to understand. If doubt exists about the meaning of responses, it is very important to clarify with the help of a carer or family member who knows the patient well.

- Carers and relatives

It is essential to complete the psychiatric history and assessment with the help of someone who knows the person well, a carer or relative. It is often necessary to collate details from several informants.

2. The Mental State Examination (MSE)

The MSE for adults with an ID is essentially similar to that taken for adults without an ID. However, in general, because of the communication problems described before that people with ID frequently have, it is often difficult to elicit accurately certain psychopathological presentations. It is important to note the following:

- Abnormal thought content

Anxiety and phobias: while the cognitive features of anxiety disorders are infrequently elicited in adults with ID, behavioural features are often seen. Irritability and restlessness are more commonly observed as symptoms of anxiety.

Obsessional symptoms: it is very difficult to obtain a clear description of obsessions being the product of a person's own mind, for example. Resistance is often found to be minimal, especially if the obsessions are long-standing.

Depersonalisation and derealisation: people with ID are frequently unable to describe these complex cognitive phenomena.

Psychotic thoughts: people with ID are prone to giving complaint answers as mentioned previously. Therefore it is quite possible to "convince" a person with ID that their beliefs are untrue. A better indicator of delusions is when the false belief is repeatedly stated. The use of open-ended, non leading questions is very important in this instance. It is also significant to remember that the content of the delusional beliefs is usually developmentally appropriate for the person's overall ability. Sometimes, beliefs that, on the surface, appear to be delusional, may simply be a reflection of overall cognitive development of the patient. This discernment requires careful evaluation during the interview. In general, complex psychotic symptoms such as delusional perceptions are infrequently found, due to the difficulty in eliciting such phenomena in people with limited verbal and intellectual skills.

- Abnormal thought form

People with ID may be more at risk of presenting with fragmentation of thought processes, sometimes precipitated by anxiety or depression. This may present in a similar fashion to formal thought disorder. A careful assessment, with collateral information, will help distinguish these presentations.

- Cognitive assessment

The diagnosis of ID is based on the person having an intelligence quotient below 70, together with continued impairment in adaptive behavioural/social functioning, and with onset during the developmental phase (before the age of 18 years). Specific assessment procedures and tools need to be utilised to accurately diagnose levels of ID, the description of which is beyond the scope of this text. The cognitive assessment already described in the Older Adult section is largely appropriate for the use in people with ID, but may need to be simplified depending on the level of ability of the person with ID.

- Functional analysis

Changes in behaviour may not signify mental illness, but may be due to learned manipulation of the environment, or the behaviour may be acting as a form of communication. A functional analysis of behaviour is frequently needed to ensure accurate diagnosis.

3. Diagnosis and Diagnostic Classification

Assessment aims not only to detect the presence of psychiatric illness and make a diagnosis, but also to identify the features that make a person vulnerable to them. Any therapeutic interventions must take into account a number of factors, including the patient's wishes, the diagnosis and vulnerability factors including psychological (for instance characteristic ways of thinking), biological (such as genetic predisposition or medication) and social (including environmental factors). Some of these vulnerability factors (such as brain damage) cannot be changed, but others (such as an optimal control of Epilepsy) can and should form part of the care plan. The introduction of operational criteria in ICD-10 (World Health Organization, 1992) and DSM-IV (American Psychiatric Association, 1994) and the use of structured and semi-structured interviews, such as the *Psychiatric Assessment Schedule for Adults with Developmental Disability* (PAS-ADD), have significantly increased the reliability of the diagnostic process in psychiatry.

The National Association for the Dually Diagnosed (NADD) in the USA, in association with the APA, developed the *Diagnostic Manual -- Intellectual Disability (DM-ID): A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability*. This offers a summary of diagnostic criteria, a review of the literature and research and an evaluation of the strength of evidence supporting the literature conclusions, a discussion of the aetiology and pathogenesis of the disorders, and adaptations of the diagnostic criteria for the ID population.

Again for those with moderate to severe ID, the *Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation* (DC-LD; Royal College of Psychiatrists, 2001) describes criteria for the diagnostic classification of mental health problems based on a consensus of current practice and opinion among psychiatrists working with people with ID. It is a multi-axial system that is being used alongside ICD-10. When appropriate, ICD-10 criteria should be used, as in most individuals with mild ID. A hierarchical approach to diagnosis is adopted:

HIERACHICAL DIAGNOSTIC DC-LD CLASSIFICATION:

Axis I: Severity of the Intellectual Disability

Axis II: Cause of the Intellectual Disability

Axis III: Psychiatric Disorders

DC-LD Level A: Developmental Disorders (such as autism)

DC-LD Level B: Psychiatric illness

DC-LD Level C: Personality Disorders

DC-LD Level D: Problem Behaviours

DC-LD Level E: Other Disorders

MENTAL ILLNESS

Mental illness and ID have been distinguished since at least medieval times but the fact that both could coexist in the same individual has only been appreciated more recently. This phenomenon is sometimes called dual diagnosis. Mental illness can be difficult to diagnose in people with an ID for the following reasons:

- Psychiatric illness may present non-specifically as behavioural disorder (e.g. aggression, self-injury, withdrawal and stereotypies).
- Physical illness may also present with emotional or behavioural symptoms.
- All symptoms may be attributed to the intellectual disability per se, rather than any additional disorder (this is known as diagnostic overshadowing).
- Although all people have communication skills, a communication barrier may exist between doctor and the patient with ID.
- Therefore a change in behaviour or a change in level of functioning in someone with ID should always be taken seriously and merits further investigation

1. Aetiology and risk factors of mental illness

There are many biological, psychological and social factors that contribute to the aetiology of mental illness in people with ID. Many of the factors are the same as in the general population and it is their interaction that is important in creating the particular vulnerability to developing mental illness. Those with ID tend to have more factors present and fewer resources to deal with them. Some of the factors, which can contribute to the development of mental illness in people with ID, are:

Biological factors:

- Brain damage (epilepsy, congenital disorders)
- Specific abnormalities (Prader-Willi syndrome, Lesch Nyhan syndrome, Fragile X)
- Family history of mental illness or learning disability/other brain disorders
- Iatrogenic (anti-epileptics, other compounds)
- Communication and sensory impairments

Psychological factors:

- Childhood experiences (separation, rejection, overprotection, abuse)
- Poor personality development (lack of self esteem, dependency, low expectations)
- Life Events (difficulty in making and maintaining relationships, labelling, bereavement, institutionalisation)
- Societal reactions (stigma, isolation, poor support, abuse)

Social factors:

- Limited choice of occupation
- Social isolation and limited peer relationships
- Lack of role models in developing adaptive skills

2. Epidemiology and characteristics of mental illness in people with ID

Mental illness is in general significantly more common in people with ID than it is in the general population, both in children and in adults. The co-occurrence of psychiatric illness with ID has been well established, and people with intellectual disabilities are more likely to suffer from mental ill health

(including behavioural disorders, personality disorders, autistic-spectrum disorders and attention-deficit hyperactivity disorder). (Debeaux, 2001)

The arrival of effective medical and psychosocial treatments for psychiatric disorders makes their diagnosis in those with ID all the more pressing. It is also essential that the development and delivery of clinical services hold what is known as prevention and minimization of those disturbances.

Mental Disorder	Epidemiology	Characteristics
Schizophrenia	Prevalence of 3% (3x general population) Associated with velocardiofacial syndrome	Difficult to diagnose in people with IQ<45. Psychotic phenomena tend to be simpler, and thought alienation less common. Bizarre behaviours and adaptive regression can occur
Bipolar Affective Disorder	More common than general population	It can be diagnosed whatever the degree of disability. In manic states, irritability is common. Recording behavioural correlates of mood can help to establish the cyclical nature of the disorder, and be used to monitor treatment.
Depression	Depression and anxiety up to four times more common in people with ID compared to the general population Associated with Down's syndrome	Often missed in people with ID because they are less likely to complain of low mood. 'Biological' symptoms are important in making the diagnosis
Prolonged grief/ Adjustment disorder	Common	Carers often unaware, problems often attributed to other causes
Acute confusional states (delirium)	More common, especially people with more severe disability or coexistent dementia.	Due to physical illness which will need diagnosis and treatment
Dementia	More prevalent than in general population (14% v. 5% in those over 65)	Psychotic symptoms and epilepsy may be a feature. Strong association with Down's syndrome, where it presents earlier.
Autism	Prevalence 4.9:10.000, female: male = 1: 4 ¾ of people with autism have ID Associated with Fragile X, Tuberous Sclerosis and phenylketonuria.	Developmental disorder that is apparent by the age of three. Features include triad of abnormal social interaction, including a particular lack of empathy, abnormal communication (e.g. echolalia, pronoun reversal), stereotyped patterns of behaviour and adherence to routines

3. Psychotic illness

The prevalence of psychotic symptoms in adults with ID is higher than in the general population. The prevalence of schizophrenia in the general population is around 1% while in the ID population is about 3%. Point prevalence rates of psychotic disorder (including schizoaffective disorder) have been found to be 5.8% in adults with mild ID and 3.5% in those with moderate/severe ID.

Assessment, diagnosis and management of psychosis in ID would follow a similar format to that in adults without an ID but adults with moderate/severe ID are more likely to have communication problems and cognitive deficits, which may pose some difficulties for thorough assessment. In those patients it could be more difficult to elicit all the symptoms required for a diagnosis using ICD-10 or DSM-IV. Psychosis is therefore more likely to be defined in a broader term in the ID population than in the general population.

Definitions within non-affective psychotic disorders in DC-LD include:

- Schizophrenic/Delusional episode or disorder
- Schizoaffective episode or disorder
- Other non-affective psychotic disorders

As opposed to the following types of psychotic disorders included in ICD-10 code and that can be specified in those with mild/borderline ID:

- Schizophrenia
- Delusional Disorder
- Acute or transient psychotic disorders
- Induced delusional disorder
- Schizoaffective disorder

A DC-LD guideline gives a summary of the symptom criteria required for a diagnosis of Schizophrenic/delusional episode:

A. *The symptoms/signs are not a direct consequence of any other psychiatric or physical disorder or a result of prescribed or illegal drugs or alcohol.*

B. The criteria for schizoaffective episode are not met. (In DC-LD, unlike ICD-10, a diagnosis of schizoaffective disorder trumps a diagnosis of schizophrenic/delusional disorder).

C. One of item groups 1, 2 or 3 are met:

1. One of the following symptoms present on most days for at least two weeks:
 - a. Third-person auditory hallucinations.
 - b. Hallucinatory voices coming from some part of the body.
 - c. Impossible/fantastic delusions (delusions that are culturally inappropriate and completely impossible).
 - d. Thought insertion or withdrawal or broadcasting, or thought echo or delusions of control, influence or passivity, or delusional perception or hallucinatory voices giving a running commentary.
2. One of following present for most of the time during one month, or some time every day for at least a month:
 - a. Delusions that are not mood congruent.
 - b. Hallucinations (in any sensory modality) that are not mood congruent.
3. Two of the following present on most days for at least two weeks:
 - a. Delusions which are not mood congruent.
 - b. Hallucinations which are not mood congruent.
 - c. Catatonic symptoms.
 - d. Negative symptoms, where there is definite evidence that this is a change from the individual's premorbid state.
 - e. Disordered form of thought, where is definite evidence that this is a change from the individual's premorbid state.

It is important to be aware of some other diagnosis that might present with similar symptoms to psychosis and that constitute the differential diagnosis:

- Physical illness: epilepsy, infections, endocrines causes, hearing or visual impairments, pain or discomfort.
- Drug or alcohol-related causes.
- Other psychiatric conditions including: affective illness, anxiety disorders, and post-traumatic stress disorder.
- Dementia.
- Autistic Spectrum Disorder.
- Other differential diagnosis such as challenging behaviours, or ID itself, can sometimes be misdiagnosed as psychosis.

An adequate mental health assessment should always take into account the individual's developmental level and it should include a history from the patient and a mental state examination, a detailed collateral history and a risk assessment. Physical examination and investigations are relevant, including blood test, septic screen if indicated and CT/MRI and EEG if indicated and no contraindications for the patient.

There are also useful checklists that can be used along with the above to identify psychiatric disorders in people with ID such as the *Reiss screen*, the Mini PAS-ADDs (*Mini Psychiatric Assessment Schedules for Adults with Developmental Disorders*), the DASH-II (*Diagnostic Assessment for the Severely Handicapped-II*) and the ADD (*Assessment of Dual Diagnosis*). These are useful tools as general indicators but less useful at determining the nature of the illness (http://www.ets.org/disabilities/documentation/documenting_learning_disabilities).

4. Affective disorders

Depression

Point prevalence of depression in those with ID is higher than in the general population. (Debeaux, 2008) People with Down's syndrome are more likely to be diagnosed as having a depressive disorder than those with ID due to other causes. The clinical features of depression in adults with ID vary with the level of disability. Those with mild ID show the same symptoms as their non-disabled peers. In those with more-severe forms of ID, somatic symptoms and their behavioural correlates, such as changes in activity levels, diurnal mood variation, sleep and appetite changes, and social withdrawal are suggestive of affective disorders. Regression to increased dependency, psychomotor agitation, increased irritability, worsening of existing behavioural and self-injurious behaviours, reduced communication and social isolation, catatonic features and visual hallucinations are more common in this group. Suicidal thoughts and behaviours are thought seldom occur in people with depression and ID, as they might not be able to form such an intention. Negative automatic thoughts and feelings of hopelessness can be ascertained in people with mild ID. As with psychosis, depression may be a component part of the psychiatric phenotype of genetic syndromes associated with ID e.g. fragile X syndrome.

Bipolar affective disorder

The lifetime prevalence rate of bipolar disorder is 1% in those without an ID. Higher prevalence is encountered in the ID population. Changes in affect and activity levels can be observed and reported by people with mania and mild to even very severe intellectual disabilities and their carers. The mania rating scale items of the DASH-II screening instrument for those with ID ('restless or agitated', 'decreased need for sleep', 'irritable', 'easily distracted', 'extremely happy or cheerful for no obvious reason', 'talks loudly and quickly') demonstrate good internal correlation and specificity with the mania DSM-IV diagnosis. Pressure of speech rather than flight of ideas, increased and decreased appetite, echolalia, crying and over-activity might be more common in the ID population with bipolar illness. Mixed affective states and rapid cycling forms (more than four episodes a year) of bipolar affective disorder might be more common in

those with ID. In Down's syndrome, mania is very uncommon among women, whereas in the general population the male: female ratio is equal. Interestingly, those with Down's syndrome less frequently have a positive family history. In the general population, rapid cycling forms are seen more commonly in women, but in those with ID, the gender ratio is equal.

Persistent mood disorders

There are few studies of dysthymia, which is probably underdiagnosed, in those with ID. Similarly, cyclothymia (persistent mood swings not meeting severity criteria for affective disorders) has as yet received little attention in this population.

5. Anxiety disorder

Panic Disorder and Generalized Anxiety Disorder

Over-activity, panic attacks, agoraphobia, sexual dysfunction, mood changes, depersonalisation and derealisation, disruptive behaviours (including aggression and self-mutilation), somatic complaints, and sleep and appetite disturbance are all common symptoms of anxiety in the ID population. In mild ID, symptoms of generalised anxiety disorder are similar to those in the general population, with increased 'brooding', somatic complaints and sleep disorder. In more severe ID, only the behavioural symptoms associated with anxiety can be reliably assessed, ruling out many core psychological symptoms of the disorder. Comorbidity with other psychiatric illnesses such as depression is common. High levels of anxiety are thought to be part of the behavioural psychiatric phenotype in William's syndrome.

Obsessive Compulsive Disorder

Compulsive behaviours have reported frequencies of 3.5% in adults with mild ID and 40% in adults with severe ID. Ordering compulsions are the most prevalent in the ID group. Complex cognitive experiences such as the recognition that the thoughts or acts are under self-control may be impossible to identify in a person with ID. Compulsions are significantly associated with stereotypies and self-injurious behaviour. Obsessions and compulsions can arise in a number of disorders other than obsessive-compulsive disorder, such as depression and pervasive developmental disorder. They are also associated with specific syndromes such as Prader-Willi syndrome. Some specific stereotyped movements have been associated with disorders such as Rett syndrome (hand-wringing movements in front of the body) and Smith-Magenis syndrome (body self-hugging, self-biting). Although obsessions and compulsions may need pharmacological treatment in individuals with Prader-Willi syndrome, the effectiveness of serotonin reuptake inhibitors in the treatment of stereotyped movements in Rett syndrome and Smith-Magenis syndrome is less established.

Adjustment disorder and post-traumatic stress disorder

Children and adults with ID are vulnerable to emotional, physical and sexual abuse. The risk of posttraumatic stress disorder and adjustment disorder is therefore likely to be significantly increased.

Eating disorders

1–19% of adults with ID living in the community and 3–42% of those living in institutions have an eating disorder, with higher rates in those with more-severe ID. Eating disorder research in those with ID has covered pica, regurgitation, psychogenic vomiting, food faddiness or refusal, psychogenic loss of appetite, binge eating disorders and anorexia nervosa. In individuals with ID living in the community, deviant eating behaviour is more likely to occur in those with a comorbid psychiatric disorder and to be associated with physical and social comorbidity. However, the impact of eating disorders on weight, physical and mental health and social functioning in the ID population has not yet been adequately addressed.

MANAGEMENT OF MENTAL HEALTH (Pharmacological, Psychological and community care interventions)

Management of Psychosis in ID

Management of psychosis in ID is similar to that of those without ID, and can be considered using a biopsychosocial approach. In the acute phase, management usually focuses in accessing services, ensuring safety of the patient and others and initiation of medication. After resolution of the acute phase, management is more likely to focus on maintaining good mental health, insight-related work and relapse prevention planning.

Evidence for the effectiveness of antipsychotic medication in people with these disorders and ID rests mainly on extrapolation of findings from general adult psychiatry. Treatments should be tailored to the individual, and so take into account any co-existing medical conditions such as epilepsy, other drugs being taken and any other particular requirements. The National Institute for Clinical Excellence (NICE) guidelines for schizophrenia (update 2009) suggests that people with schizophrenia have a physical health review by their GP at least once a year and an ECG prior to starting on antipsychotics and at regular intervals thereafter to monitor any abnormalities, in particular any QT interval prolongation. Monitoring for prevention of metabolic syndrome is also recommended. Small studies in the literature show that clozapine appears to be efficacious and safe in people with ID. However, careful monitoring of side effects is recommended. A Cochrane review in 2004 did not find any significant randomized controlled trials that examined antipsychotic medication versus placebo in people with psychosis and ID. There is still a need for further research in the field.

With regards to psychological treatment in psychosis we should mention that for a long time the role of psychology in ID was to provide therapy in the form of behavioural therapy to manage behaviours deemed undesirable in the large long-stay institutions. Historically the emotional lives of those with an ID were largely neglected. With the gradual closure of the long stay units and the focus in community care, the role of psychology has expanded enormously. Interventions such as cognitive-behavioural therapy, psychodynamic and systemic therapy do deserve attention in those with mild or borderline IQ, but have seldom been formally researched in the moderate and severe ID population. Assessment and management of expressed emotion in families and professional carers can also be beneficial. Psychological risk factors common to many people with ID include a history of unstable attachments, learned helplessness, low self-esteem, limited social skills and poor problem solving strategies. Social and environmental risk factors relate to social barriers and dependence support from carers, and may include stigma and segregation, over-protection, lack of opportunities, neglect and abuse, limited social networks and poorly managed changes and losses.

Respite care and rehabilitation for those with more chronic illnesses, including the use of day services, should be part of a comprehensive long-term person-centred management plan. Practical social interventions, tailored to the individual's needs, are important in order to support both the patient and the support network.

Management of Mood and Anxiety disorders in ID

The National Institute of Clinical Excellence (NICE) in the UK has provided clinical guidelines for the identification, management and treatment of anxiety and mood disorders (panic disorder, with and without agoraphobia, generalized anxiety disorder, PTSD, obsessive-compulsive disorder, depression and bipolar disorder). These guidelines, with adaptations for those individuals with greater communication difficulties, are also applicable to those with an ID. Treatment as for the general population is appropriate with the following cautions:

- Treatment with medication: start low, go slow and change one medication at a time, as there is higher frequency of idiosyncratic responses to psychotropic drugs.

- Psychological therapies: adapted according to the individual's cognitive, communication and concentration capacities.
- Multi-modal interventions, for example psychotherapy, sensory therapy, behavioural therapy, stress management, attention to communication and medication may be necessary.
- Client, family and carers need to agree the treatment plan and where more than one intervention is being offered; they need to understand the focus of each intervention. Where different medications are being used simultaneously, the reason for each needs to be explained.
- Clinical relapse may be due to different cause from the aetiology for which the medications or other interventions are being targeted. It is wise therefore to have a crisis plan mapped ahead of time in order to address safety and other issues at these times.

The full range of bio-psychosocial treatments should be available for people with ID. For those with the most severe forms of depression and those with suicidal intent, hospital admission needs to be considered. Antidepressants can be effective in those with an ID and depressive disorder, but may have considerable side effects, including increased irritability. Electroconvulsive therapy might be effective as an adjunct to treatment in the acute phase of the most severe acute and otherwise nonresponsive episodes of depression in those with ID. Antipsychotics might need to be used for the acute phase of bipolar illness. A mood stabilizer then should be used as maintenance therapy to prevent relapse. There is some evidence that anxiolytic drugs such as buspirone are effective in treating those with ID and anxiety. Treatment with selective serotonin reuptake inhibitors may be beneficial in obsessive-compulsive disorder, as may various behavioural techniques. Social treatments can include interventions in the social network and helping people to find meaningful occupation and develop their skills. It can mean ensuring that people are treated with appropriate dignity and respect and are able to make choices in their lives.

ESSENTIAL HEALTHCARE IN ID

ID is by definition related to some form of cerebral trauma in the developmental period. This is not only confined to just those areas of the brain responsible for cognitive and social functioning but also associated to a variety of physical impairments that can lead to additional health needs over and above those experienced by the general population. There is generally a graduation with the prevalence and severity of physical problems usually increasing from people with mild to more severe ID. Common health deficits in people with ID are highlighted in the box below.

- Sight problems
- Hearing difficulties
- Dental diseases
- Epilepsy
- Psychiatric illness
- Eating Disorders
- Sleeping Disorders

- Challenging behaviours
- Obesity
- Poor diet
- Communication Problems
- Respiratory Function Problems
- Skin conditions
- Foot Care Problems

Structured health checks in primary care can identify clinically significant previously unrecognized morbidity among adults with intellectual disabilities and an annual health check is recommendable in people with ID. Psychiatric disorders can also have a significant impact on the physical health of a person with ID. For example, depression and psychosis may predispose to poor compliance with medication, and chronic psychiatric illness is associated with poor physical health and morbidity.

EPILEPSY

Rates of epilepsy are much higher in the ID population than in the general population and an underlying brain abnormality is often the common pathway in both. The prevalence in the general population is 0.5%, in mild ID it is 4%, in moderate/severe ID 30%, and in profound ID it is 50%. A third of adolescents with autism develop epilepsy, and it is associated with other syndromes such as Tuberos Sclerosis, Sturge-Weber syndrome and Rett's syndrome. Severe epilepsy and ID may lead to progressive deterioration or sudden death. Diagnostic overshadowing may occur when assessing epilepsy. "Strange behaviour" has a wide differential e.g. epilepsy, mental illness, a harmless or harmful habit that the individual has developed over time, an attempt at communication, a response to a stressful situation, a side effect of a drug. That is why a thorough full psychiatric and medical history and mental state is required. An informant is essential especially as witness to the seizures and a full description of seizure is required, i.e. frequency, duration, severity (e.g. led to injury, impact on life in general).

Epilepsy is associated with increased prevalence of nearly all forms of psychiatric disorder. Possible mechanisms include greater social disadvantage, chronic potentially life threatening illness, accidents, head injuries, self-esteem issues, dependency on others. Temporal lobe epilepsy presents often with psychiatric symptoms. Some studies report that rates of psychosis are higher in those with milder disability and epilepsy, whereas depression rates are higher in those with severe disability. A complex relationship exists between poor impulse control, epilepsy and socio-cultural factors. Interestingly, 'Forced Normalisation' is an uncertain phenomenon but relatives/carers frequently report that patient is improved in mental health terms when fit control not so optimal.

Epilepsy seems to present as more complex in the ID group than in the general population and is often treatment resistant. Studies report generalized tonic-clonic seizures as the most common type in this group and complex partial seizures as the most common in people with ID and autism. It is important to mention that non-epileptic seizures (pseudo seizures) are more common in people with ID. Possible mechanisms may be the limited communication skills that people with ID have, their crude expression of emotional conflicts and increased suggestibility. However, people with genuine epilepsy may also have pseudo seizures.

Epilepsy and its treatment can have a profound effect on individuals with ID. This can impact on physical health, psychological health and mortality, and in turn also could have an impact on the families and carers of these individuals. Anti-epileptic drugs of proven efficacy in the general population are also effective in people with ID. However, adverse reactions to anti-epileptic drugs are seen more frequently than in the general population, being somnolence and ataxia the most common in people with ID. Most antiepileptic drugs have agitation or mental illness as an associated side effect, although carbamazepine, lamotrigine and

sodium valproate are also used as mood stabilisers. Finally, the treatment of epilepsy may also reduce cognitive ability (both drugs and surgery).

MENTAL HEALTH ISSUES OF AUTISM

Autism spectrum disorder (ASD) is the term currently used for people with ICD-10 defined childhood autism, Asperger's syndrome or atypical autism. The cause of ASD is unknown but best considered as a multifactorial illness. The distribution of ASD within families indicates that it cannot be caused by a single gene but must involve the interaction of several. Some people with ASD without a family history of same would have a personal history of perinatal or childhood neurological complication.

The ICD-10 criteria for diagnosing ASD can be summarized as follows: if the person meets the following criteria and onset before age 3, we can talk of childhood autism; if only meet two of the criteria or onset after age 3, it is called atypical autism; and if no delay in development of communication or cognitive development, a diagnosis of Asperger's syndrome can be made. The main characteristic features for diagnosis of ASD are:

-Qualitative impairments in reciprocal social interaction:

- Lack of responses to other's emotions.
- Lack of modulation of behaviour according to social context.
- Poor use of social signals.
- Poor use of non-verbal signals to regulate social interactions.
- Weak integration of social, emotional and communicative behaviours.
- Lack of socio-emotional reciprocity.
- Failure to develop peer relationships involving sharing.

-Qualitative impairment in communication:

- Delay in development of language (without attempts to use other methods of communication).
- Lack of social usage of language skills.
- Repetitive speech.
- Poor synchrony and reciprocity in conversational interchange.
- Lack of emotional response to other people's verbal and non-verbal overtures.
- Poor flexibility in language expression.
- Impaired use of cadence or emphasis to modulate communication.
- Impaired use of gesture to augment spoken communication.
- Impairment in make-believe and social imitative play.
- Relative lack of creativity and fantasy in thought processes.

-Restricted, repetitive and stereotyped patterns of behaviour:

- Tendency to impose rigidity and routine on day-to-day living.
- Resistance to change in environment or routines
- Attachment to unusual objects, or interests.
- Non-functional routines.
- Interest in non-functional elements of objects.
- Motor stereotypies.

The main problem in diagnosing mental health illness in ASD is for those with more limited communication skills and for those who cannot describe how they are feeling or what they want. However, people with ASD do have the same emotional needs that people with no ASD. They often report feeling isolated and wanting to have friends, though they may not have the skills necessary to form relationships. People with ASD also find particularly unsettling the normal changes in life such as leaving school, a different job or an argument with a friend. The impact of those life changes in people with ASD can be

quite dramatic, even precipitating the development of mental health illness, which requires proper assessment and management.

Anxiety is often more common in people with ASD than in the general population, causing all types of uncomfortable emotional feelings and physical reactions. Frequently, due to the “one shot learning” style of memory, one unpleasant experience may lead to avoidance and a phobic reaction. Most able people with ASD are also aware that they are different to other people and can develop a severe social performance anxiety and phobia. They classically have repetitive behaviours and routines that they do usually for pleasure or to calm down their anxiety. In some cases, however, they might develop obsessive-compulsive disorder.

Attention Deficit Hyperactivity Disorder (ADHD) can also coexist with a diagnosis of ASD. The difficulty is deciding whether the level of distractibility or restlessness of the person is in keeping with their general level of functioning, or more severe than should be expected. In the later, stimulant medication could be considered in combination with behavioural programmes and bearing in mind the possibility of exacerbation of epilepsy and tics.

People with ASD can suffer from unstable mood that is rapidly changing and usually dependent on a recent stressor. That type of mood instability is linked to lack of self-awareness and emotional regulation and managed most successfully with psychological support. Despite of this, the most common psychiatric disorders associated with ASD are severe depression and mania, which are usually managed with the conventional pharmacological and psychological strategies. Hypomania and agitated depression are particularly difficult to distinguish in a person with ASD. The most common prominent feature is the degree of sexual activity, which is associated with hypomania but very unusual in agitated depression.

With regards to psychosis in ASD it is important to say that there might be an over-diagnosis of schizophrenia in people with ASD due to the rate’s misinterpretation of odd beliefs and strange habits as psychotic or delusional thinking. It is common that with anxiety and stress at times of crises develops into an acute and transient psychotic episode. People with ASD can also present as quite paranoid towards other people, mostly due to not being able to understand what is going on around them.

No conclusion has been finalised on whether to include personality disorder diagnosis in people with ASD. People with ASD appear to have much greater problems controlling impulses, mostly due to not learning many of the self-controls gained during social skill development.

CHALLENGING BEHAVIOUR

People with ID are sometimes described as having ‘Challenging Behaviour’. This is defined as ‘culturally abnormal behaviour of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behaviour which is likely to limit use of, or result in the person being denied access to, ordinary community facilities’.(Emerson, 2001) Challenging behaviour can have a number of different causes, including psychiatric and physical illness, but it is not a medical diagnosis in itself. For example, self-injurious behaviour is a common type of ‘challenging behaviour’ occurring in 8-15% of those with ID in institutions and 2-4% in the community; 50% of those with self-injurious behaviour have additional behavioural disorders. It can be caused by mental illness such as depression or psychotic disorders, or by environmental factors such as lack of sensory stimulation. It is also associated with specific syndromes, i.e. Lesch-Nyhan syndrome and several neurotransmitters have also been implicated in its aetiology, e.g. serotonin deficiency.

Generally challenging behaviour presents as a communication of the individual’s needs, whether intentionally or unintentionally. That behaviour that has been labeled as challenging may reflect the lack of resources and the label may reflect the needs of the network rather than the individual. However, challenging behaviour is the most common reason for referral to a psychiatrist in those with ID. The presentation may have physical, psychological or social underpinnings or a combination of the three and these may have an impact on the treatment and management strategies. At least four types of relationship of clinical significance between challenging behaviour and psychiatric disorder have been identified:

- (1) Family factors associated with the development of challenging behaviour appear to be similar to those associated with the development of conduct disorder;

- (2) Challenging behaviours may represent the atypical presentation of an underlying psychiatric disorder; some forms of self-injurious behaviour may represent an obsessive–compulsive disorder;
- (3) Challenging behaviours may occur as secondary features of psychiatric disorders among those with severe ID;
- (4) Psychiatric disorders may establish a motivational basis for the expression of challenging behaviours, maintained by operant behavioural processes.

A thorough process of assessment is necessary to then be able to manage a case successfully. The assessment usually would include several interviews with professionals, carers and relatives. Physical examination and investigations are required and for more complex cases a deep understanding of the social and systemic context the individual lives in can be quite revealing. Some of the common physical and mental disorders associated with challenging behaviours are:

Diagnosed physical complaints: -Dental pain

-Urinary tract infection

-Respiratory infections

-Gastritis/gastric ulcer

-Constipation

Presumptive physical complaints: -Pyrexia with evidence of local infection

-Gastro-esophageal reflux

-Gastritis

-Headache

Diagnosed mental disorders: -Anxiety disorders

-Depressive disorder

-Psychotic disorders

-Insomnia

-Hyperkinetic disorders

-Autistic disorders

Presumptive mental disorders and sub-syndromal: -Anxiety and distress

Functional assessment is an interactive process that allows a better understanding of the environment and the routines of an individual as well as what the triggers or reinforcing factors of a particular behaviour. It essentially looks at the antecedents (what is happening before the behaviour occurs) and the consequences (what happens after the behaviour) of the behaviour in an attempt to determine what its function might be. The Positive Behaviour Support (PBS: Lavigna & Donnellan, 1986) is a combined behavioural analysis and person centred approach to working with challenging behaviour. Its aim is to replace the difficult behaviour with functionally equivalent ones while looking at and changing environmental and social factors that influence the behaviour or maintain it. A proper PBS should include the following:

- Descriptions of replacement behaviours and how these should be implemented.
- Teaching functionally equivalent behaviours and communication and when and how these will be taught.
- The manipulation of setting events that leads to the person displaying challenging behaviour.
- The manipulation of antecedents and consequences to behaviour.
- How and when appropriate behaviour should be rewarded or reinforced.

With regards to treatment of challenging behaviour with pharmacological interventions it should be mentioned that a Cochrane review of antipsychotic medication for treatment of challenging behaviour confirmed that there is not clear support for drug treatment. In clinical practice though, some of the most complex cases of challenging behaviour might benefit to some extent from this type of medication.

CONSENT ISSUES

Capacity is the ability of a person to make a decision at the time it is needed. Capacity to consent is a concept that means decision specific – a person might have capacity for one sort of decision but not another. People who can't consent deserve to be treated in their best interests and relevant parties should be consulted when assessing capacity to consent e.g. relatives, carers, but they cannot consent for an adult who can't consent for him/herself. In controversial cases or where there is disagreement between parties, a Court can be asked to make a ruling. For treatment of mental disorder, the *Mental Health Act (2001)* could be used for treatment against a patient's wishes.

Despite of the general public belief, most people with ID can make decisions for themselves and do have capacity to consent in most cases. However, some people with severe or profound ID are not able to make decisions if they are complex ones, lacking therefore capacity in such cases. Capacity may also fluctuate over time, for example in the case of delirium or during the course of a relapse of a mental illness. A person can have capacity to make some more straightforward decisions and lack capacity for more complex decisions for example. For someone to have capacity the following criteria should be met. A person is considered to be lacking capacity to make a decision if they are unable to meet at least one of the following:

- Ability to understand the information relevant to the decision.
- Ability to understand the choices and weigh up the pros and cons.
- Ability to retain the information
- Ability to communicate the decision (by any means).

If a person lacks capacity, then it may be necessary to make decisions on their behalf, in their best interests. Health professionals are often driven by their aspirations to be successful with treatment or avoid complications that they have a very narrow view of the person's best interests. However, other factors should be taken into account such as:

- a. All the issues that are identified as relevant for the person who lacks capacity
- b. Likelihood of the person regaining capacity
- c. Involvement of the person in the decision process as much as possible
- d. Consulting other people close to the person lacking capacity in order to find out about past wishes, interests, views and beliefs.

In Ireland, the *Mental Capacity Bill of 2008* reformed the laws that protect adults who, due to illness, accident or intellectual disability, are unable to make decisions for themselves or exercise their legal capacity. The Bill replaced the Wards of Court system, which was the existing mechanism for managing the affairs of persons who lack decision-making capacity.

CLINICAL SYNDROMES ASSOCIATED WITH ID

The most common syndromes associated with ID are summarized below. We highlight their main clinical and phenotypic characteristics and provide information regarding website links for further reading.

Down's Syndrome

• Inheritance	Trisomy Chr 21: 94% non-disjunction, 3-5% translocation, 1-3% mosaicism
• Cognitive phenotype	Mostly moderate ID (IQ 20-75, mean 50)
• Psychiatric phenotype	Alzheimer's dementia (45% over 45 years), Depression and OCD.
• Behavioural phenotype	Sociable, good-natured, stubborn.
• CNS	Epilepsy (mostly linked to Alzheimer's).
• Cardio-vascular	Congenital heart disease (40-60%), AV canal defect, tetralogy of Fallot.
• Endocrine	Thyroid disorder in 25% (mostly hypothyroidism)
• Audiovisual	Multifactorial visual and hearing impairments.
• Muscular/skeletal	Atlanto-occipital and atlanto-axial instability, hypotonia.
• Other	Blood dyscrasias, skin disorders, gastrointestinal disorders, genitor-urinary disorders, obesity, sleep apnoea, recurrent infections, leukaemia.
• Weblink	www.downs-syndrome.org.uk

Prader Willi Syndrome

• Inheritance	70% sporadic (deletion on Chr 15 of paternal origin), 25% uniparental disomy (2 maternal Chr 15)-IMPRINTING
• Cognitive phenotype	Normal IQ or Mild-moderate ID
• Psychiatric phenotype	Psychosis, OCD, Anxiety.
• Behavioural phenotype	Hyperphagia, self-injury (skin picking), stubborn, poor impulse control, sleep problems, emotional lability.
• CNS	Microcephaly
• Cardio-vascular	Heart failure secondary to obesity may arise
• Endocrine	Diabetes secondary to obesity
• Audiovisual	
• Muscular/skeletal	Short stature, scoliosis, hypotonia, small extremities.

• Other	Severe obesity, undescended testes, hypogonadism, sleep apnoea.
• Weblink	www.pwsa.co.uk

Fragile X Syndrome

• Inheritance	X-linked (FMR-1 gene has expansion of trinucleotide repeats at fragile site on X Chr)-ANTICIPATION.
• Cognitive phenotype	Borderline, mild or moderate ID (females tend to have higher IQ than males).
• Psychiatric phenotype	Depression
• Behavioural phenotype	Hyperactivity, social avoidance, gaze aversion, shyness, autistic features, hand flapping and biting.
• CNS	Epilepsy
• Cardio-vascular	Aortic dilation, mitral valve prolapse.
• Endocrine	
• Audiovisual	Multifactorial visual and hearing impairment.
• Muscular/skeletal	Connective tissue disorder, scoliosis, high-arched palate, macrocephaly.
• Other	Hernia, large ears, macro-orchidism, speech and language abnormalities.
• Weblink	www.fragilex.org

Velocardio Facial Syndrome 22q 11

• Inheritance	Sporadic microdeletion in Chr 22, maybe autosomal dominant.
• Cognitive phenotype	ID in 30% of cases, usually mild ID.
• Psychiatric phenotype	Schizophreniform psychosis (less than 25%), Bipolar affective disorder, Anxiety, Depression.
• Behavioural phenotype	Hyperactivity, autistic features.
• CNS	
• Cardio-vascular	Congenital heart disease (more than 70%), especially conotruncal malformations.
• Endocrine	Hypocalcaemia
• Audiovisual	Multifactorial hearing impairment.
• Muscular/skeletal	Polydactyly
• Other	Cleft lip/palate, thymic dysplasia, hypernasal speech, immune problems, characteristic facies, dysphagia, renal abnormalities, and gastric reflux.
• Weblink	www.geneclinics.org/profiles/22q11deletion

Phenylketonuria

• Inheritance	Autosomal recessive (inborn error of metabolism Chr 12).
• Cognitive phenotype	Variable IQ and social disability: progressive brain damage in untreated PKU with a 50 point drop in IQ by one year.

• Psychiatric phenotype	Anxiety
• Behavioural phenotype	Autism, poor concentration, hyperactivity, irritability.
• CNS	Microcephaly, epilepsy, spasticity.
• Cardio-vascular	Poor peripheral circulation.
• Endocrine	
• Audiovisual	
• Muscular/skeletal	Hypotonia
• Other	Variable clinical picture depending on deficiency of phenylalanine hydroxylase enzyme, eczema, light skin pigmentation.
• Weblink	www.ncbi.nlm.nih.gov

Neurofibromatosis

• Inheritance	Usually Autosomal dominant but can be also sporadic (Chr 17 and 22).
• Cognitive phenotype	Variable IQ (ID in less than 10%).
• Psychiatric phenotype	
• Behavioural phenotype	Hyperactivity
• CNS	10% have epilepsy depending on the sites of tumours.
• Cardio-vascular	Cardiac problems depending on the site of tumours.
• Endocrine	Depending on the site of glioma.
• Audiovisual	Glioma affecting visual and hearing, iris hamartomas.
• Muscular/skeletal	Skeletal abnormalities (kyphoscoliosis).
• Other	Variable picture depending on tumour sites, tumours are susceptible to malignant change.
• Weblink	www.ninds.nih.gov

Tuberous Sclerosis

• Inheritance	Usually sporadic, can be autosomal dominant (Chr 9, 11, 16).
• Cognitive phenotype	Variable IQ, 50% have ID (mostly severe-profound).
• Psychiatric phenotype	Depression, Anxiety, Specific phobias, Psychosis (epilepsy related).
• Behavioural phenotype	Autistic features, hyperactivity, self-injury, sleep problems, aggression.
• CNS	Epilepsy in 70% of cases, cerebral astrocytomas.
• Cardio-vascular	Cardiac rhabdomyomas.
• Endocrine	
• Audiovisual	Retinal tumours.

• Muscular/skeletal	
• Other	Renal and lung hamartomas, polycystic kidneys, skin lesions (fibromas, fibrous plaques, hypomelanotic macules, adenoma sebaceum, café au lait spots).
• Weblink	www.nlm.nih.gov/medlineplus/tuberousclerosis.html www.ninds.nih.gov

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FURTHER READING

OMIM – Online Mendelian Inheritance in Man (a database to search for information about any genetic/chromosomal condition)
www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

Books Beyond Words Series

These are picture books for adults and adolescents who cannot read or who have difficulty reading. They are about difficult events people may experience, especially the emotional aspects of such events. The books actively address the problems of understanding that people with learning and communication difficulties experience. The stories are told through colour pictures, helping readers to cope with events such as going to the doctor, bereavement, sexual abuse and depression. The stylised drawings include mime and body language to communicate simple, explicit messages to the reader.

www.rcpsych.ac.uk/publications/bbw

8

Child Psychiatry

9

Aspects of Genetics

Brian O'Shea

'Most researchers cannot possibly know what it is like to grow up in a family haunted by a genetic disease – nor should we expect them to'. (Hayes, 1992)

'It has become fashionable to ascribe much psychopathology to the evils of modern society... Often imbued with political overtones... it does not take into account the obvious fact that the biological heritage of mankind extends back many millions of years'. (Trimble, 1996)

'But for every gene that codes for a protein, there are others that regulate its actions and yet others that regulate the regulators'. (LeFanu, 1999)

A gene is a part of DNA containing the message for a polypeptide sequence. Genetics⁸⁵² (Gk *gennō*, to give birth) have come to psychiatry to stay, (Emery, 1991; Murray & McGuffin, 1993; Iles, 2009) and with them have arrived a plethora of ethical and social issues, not least of which is the involvement of the commercial sector. (Tanne, 1992) Society should not become so habituated to genetic data that it ceases to try to better the environment. (Faraone ea, 1999; Foley ea, 2004) Molecular genetic techniques⁸⁵³ have been very successful in single gene disorders, which are usually rare, whereas common familial disorders provide greater difficulties because of their complex and non-mendelian patterns of transmission. (Owen & McGuffin, 1992) An abnormal gene may not function at all, as in phenylketonuria, or may malfunction, as in Huntington's disease. Nearly all genetically-influenced behaviours, be they normal or abnormal, are likely to reflect the additive effects of more than one gene (at different loci). (Plomin, 1990; Watson, 2004, p. 26) The multifactorial nature of mental illness makes simple genetic deductions about cause problematic. (Baron ea, 1990) Disorders may show variable penetrance (not all gene carriers develop the disorder), genetic heterogeneity (a number of different genetic routes leading to the same condition or syndrome), pleiotropy (the same gene is expressed differently in different people), and people who are not genetically predisposed may manifest the disorder (phenocopy). Also, psychiatric disorders have developed improved reliability as distinct from proven validity over the years, i.e. it is unclear where one clinical disorder ends and another begins. The reasons why a disorder is familial⁸⁵⁴ include genetic, early and current shared environments (e.g. the language used), learned behaviour, role modelling, etc. Geneticists divide environmental factors into *unique* (to siblings in the same family) and *common/shared* (by siblings in the same family).

Male foetuses are spontaneously aborted more often than female foetuses.

The fundamental property of single-stranded DNA is its tendency to bind to another strand consisting of a complementary base sequence⁸⁵⁵.

There are 46 chromosomes⁸⁵⁶ in 23 pairs in the human somatic cell compared to four pairs in the fruit fly *Drosophila* and over 300 pairs in some fern cells. (Gribbin, 2002, p. 542) Each chromosome contains one

⁸⁵² Term coined by the British biologist William Bateson (1861-1926) in 1909.

⁸⁵³ **Molecular genetics** investigates the chemical and physical nature of genes and how genes exert control over development, growth and physiology. Various technologies are employed. Recombinant technology (molecular cloning – foreign gene put into a host cell so that it can be replicated and studied), PCR (oligonucleotide primers, tiny bits of DNA, are made to complement the DNA on either side of the sequence on wishes to amplify), rapid genotyping using chip (containing up to a million DNA variants) technology, genomics (how the functions and interactions of genes occur), and bioinformatics (ways of using large amounts of data in the search for similar sequences and predicting gene structure and function).

⁸⁵⁴ Runs in a family.

⁸⁵⁵ Francis Crick, James Watson, and Maurice Wilkins received the 1962 Nobel Prize for discoveries concerning molecular structure of nucleic acids and their role in information transfer. There are about 3 bn bases in the human genome.

⁸⁵⁶ Walter Flemming (1843-1915) of Germany identified structures in the cell nucleus in 1879 that are known as chromosomes. Albert Levan (1905-1998, Swedish botanist) and Joe Hin Tijo (1919-2001, Javanese cytogeneticist) reported the human complement of 23

very long (in relative terms) continuous molecule of DNA (deoxyribonucleic acid). DNA consists of deoxyribose, phosphate, the purine bases adenine (A) and guanine (G), and the pyrimidine bases cytosine (C) and thymine (T). Mammalian DNA is supercoiled around proteins called histones⁸⁵⁷.

Bacteriophages are viruses that stick to bacteria and inject their DNA or RNA into the bacterial cell wherein new viruses are manufactured. The bacterial cell then dies⁸⁵⁸.

*Gene mutations*⁸⁵⁹ involve the substitution of one base for another. Commonly this change a *missense* mutation (a triplet coding for an amino acid is changed to that for another amino acid, which can have different effects on protein activity depending on the position of that amino acid within the protein molecule); about a third are *nonsense* mutations (the substitution changes the codon to a stop signal, which often reduces or stops mRNA formation or, in the cases where the stop codon is skipped over, aberrant mRNA is formed); *splice-junction* mutations (changes the way mRNA is spliced, which can have pathological consequences); and, *silent* mutations (these are not expressed phenotypically). *Point mutations* are created by changes in a single base pair (the simplest mutation) or by the deletion or insertion of one gene; if the coding region is affected then a codon may be made that leads to a missense or nonsense mutation with the production of the wrong amino acid or (because of changed sequence to a stop codon) or an incomplete protein.

Pseudogene

Mutated gene duplication incapable of translation into functional proteins

May misalign with neighbouring normal gene during meiosis

Any crossover may mutate the normal gene

E.g. mutation of gene for 21-hydroxylase causing congenital adrenal hyperplasia

A genetic disorder is one that is coded in one or more DNA segments. A genetic aberration may be hereditary or non-hereditary. RNA (ribonucleic acid) differs from DNA in that it is single-stranded instead of double-stranded, has ribose (R) instead of deoxyribose, and uracil (U) instead of thymine. RNA can hybridize with a complementary sequence of single-stranded DNA (ssDNA). RNA exists in several forms: messenger (mRNA) and transfer (tRNA) RNA. The product of the mRNA for the gene for Huntington's disease has been called 'huntingtin'. (Huntington's Disease Collaborative Research Group, 1993) This protein contains more than the normal amount of glutamine (the CAG triplet⁸⁶⁰ codes for the amino acid glutamine): uninterrupted glutamine residues known as a polyglutamine tract. Apparently, those proteins containing more than 50⁸⁶¹ glutamine molecules form tight intranuclear balls that are lethal to the cell. cDNA or complimentary DNA, libraries of which are used in research into genetic defects, is DNA produced by reverse transcription from mRNA. In other words, reverse transcriptase catalyses the synthesis of DNA from RNA and can make a complimentary copy of DNA (cDNA) from mRNA, which can then be used to synthesise a gene probe⁸⁶². A molecule of complimentary DNA (cDNA) contains the information required to make a functional protein. However, cDNA contains no introns. Genes showing high DNA sequence similarity between different species (e.g. human and fly) and that perform similar functions in such creatures are known as *orthologs*⁸⁶³.

chromosomes (46 chromosomes instead of the 48 believed to be present until then) in 1956 in *Hereditas* ('The chromosome number of man', vol. 42, pp. 1-6), three years after Watson and Crick proposed the structure of DNA.

⁸⁵⁷ I.e. histones are proteins that package DNA in chromatin (complexes of DNA and protein) inside the cell nucleus.

⁸⁵⁸ Usually it dies by lysis.

⁸⁵⁹ Errors in DNA replication or somatic mutations are nearly always repaired by DNA repair enzymes. Progeria is due to a mutation in such an enzyme.

⁸⁶⁰ Examples of disorders associated with **triplet repeats** are Huntington's disease, fragile-X syndrome, dentate-rubro-pallido-luysian atrophy, the spinocerebellar atrophies, and myotonic dystrophy.

⁸⁶¹ Authors give different figures for the number of repeats that are associated with disease. One source gives a range of 36-120 CAG repeats for affected individuals, unaffected individuals having 2-25 repeats. Another source states that under 34 repeats carries no risk, 30-40 carries 'intermediate' risk, and 41 or more repeats suggests that disease will follow if the patient lives long enough.

⁸⁶² A **gene probe** = radioactively labelled molecule that binds to target gene and can then be detected by an assay such as autoradiography.

⁸⁶³ A *homolog* is a gene that is related to another gene by descent from a common ancestral DNA sequence. It includes the *ortholog* (keeps same function) and the *paralog* (genes related by duplication within a genome; this evolves a novel function, even if it is only a slightly different one).

Genes contain exons (coding sequences) and introns (non-coding sequences⁸⁶⁴). The initial mRNA formed from a gene is precursor RNA. The part of mRNA formed from introns is excised and those parts from the exons are joined or spliced together to form the final mRNA (post-transcriptional processing). Despite being from the one gene, exons may be spliced together in different ways so that different proteins may be manufactured in different tissues. This means that organisms did not need to add many new genes over evolutionary time in order to become more complex. Abnormalities in splicing may lead to disease. The process of producing mRNA from DNA occurs inside the nucleus and is termed transcription⁸⁶⁵. RNA polymerase (RNAPol) can exist in one of three forms in eukaryotes: RNAPol I (creates ribosomal RNA, i.e. rRNA), II (creates messenger RNA, i.e. mRNA), and III (creates transport RNA, i.e. tRNA). Activator and co-activator (*transcription factors*⁸⁶⁶) proteins provide a link to distant enhancer elements in the DNA sequence and are involved in regulating both transcription and correct positioning of RNAPol at the commencement of an open reading frame, the latter being a set of codons lying between start and stop codons. In the cytoplasm (neuroplasm) each amino acid becomes attached to a particular tRNA, the latter then combining with a complimentary mRNA. Ribosomes (large complexes of ribosomal RNA [rRNA] and protein) move along the mRNA, linking up amino acids to form a polypeptide chain, a process termed translation.

The *c-fos* and *zif 268* genes are members of a class designated as *immediate early genes* (IEGs). IEGs encode transcription factors that are rapidly and transiently induced in the CNS by a variety of extracellular stimuli. They translate extracellular signals into alterations in intracellular neuronal function by regulating the expression of other genes, the latter being referred to as *late-response* or *target genes*. The IEG *fos B* may have a role in maternal care of offspring, at least in mice. (Brown et al., 1986)

There are 46 chromosomes (as 23 pairs) in human somatic cells. These are named from 1-22 in terms of decreasing length; there is also a pair of sex chromosomes, X and Y, or X and X. No known disorders are carried on the Y chromosome. A dominant trait is one that manifests in the heterozygote. A father cannot transmit an X-linked trait, be it dominant or recessive, to his son. A monoploid cell has one member of each homologous pair of chromosomes. A euploid cell contains an exact multiplication of the monoploid number of chromosomes, the normal euploid number in humans being 46, i.e. diploid (twice monoploid number). Aneuploid cells are non-euploid, such as exists in Turner's (XO) and Down's syndromes (trisomy 21⁸⁶⁷, described in 1959: 95% of Down's is trisomy 21, 4% is translocation, and 1% is mosaic where some cells are normal and others are trisomy 21). Non-disjunction occurs at or after the first zygotic division in mosaic Down's syndrome.



Down's syndrome

Copy number variation (CNV) refers to a segment⁸⁶⁸ of DNA for which copy-number differences have been found by comparing two or more genomes. Humans, being diploid, normally have 2 copies of each

⁸⁶⁴ Introns were once seen as merely evolutionary vestiges. However, they can influence the pattern of gene splicing and an intron variant may point toward a functionally important variation in another part of the gene.

⁸⁶⁵ Cells need to be able to start or stop transcription when the body is developing or when responses to external events dictate. Transcriptional factors stick to DNA in order to activate or repress this process. Additionally, hormone levels and other extracellular factors exert influences on transcription.

⁸⁶⁶ These proteins, either *activators* (increase transcriptions) or *repressors* (decrease transcriptions), recognise specific DNA sequences inside *promotor sequences* (regulatory sequences that may up- or down-stream of, or within, a gene). These factors often bind to DNA as pairs – members of the pair may be identical (*homodimers*) or non-identical (*heterodimers*). Transcription factors are required for the normal differentiation of cortical nerve cells.

⁸⁶⁷ 8 out of 10 children with **trisomy 21** will now reach at least their 60th birthday. The features/complications of this trisomy include a classic facies, mild/moderate low IQ, deafness, hypothyroidism, cardiac defects, leukaemia, duodenal atresia, and seizures.

⁸⁶⁸ Segment length may range from one kilobase to several megabases in size.

chromosomal region (1/chromosome). This may vary because of deletion or duplication.⁸⁶⁹ CNVs may have a role in autism, intellectual disability, and schizophrenia. (Guilmatre et al, 2009)

Mitosis⁸⁷⁰, the usual type of cell division, leads to an increase in the number of cells⁸⁷¹ for body growth and cell replacement; all chromosomes are duplicated and distributed equally to two daughter nuclei, each containing the same set of chromosomes as the parent nucleus. Mitosis is artificially divided into interphase⁸⁷², prophase, metaphase, anaphase and telophase. Cell division is completed by cleavage of the cytoplasm.

Meiosis involves gamete production (gametogenesis), both sperm and egg. It is also called reduction division, because the number of chromosomes in the cells produced by meiosis is halved. Put another way, each gamete receives either of a pair of homologous (matching) chromosomes. Four haploid gametes are present at the end of meiosis: in the case of the male germline these are retained as sperm, whereas in the female germline only one is retained as an ovum, the other three forming polar bodies. The process of meiosis consists of 2 steps, each with a prophase, metaphase, anaphase and telophase. *Crossing over*, the exchange of genetic material between chromatids of maternal and paternal homologous chromosomes, may occur when these chromosomes are paired during prophase of the first meiotic division.

Most fetuses with chromosomal abnormalities do not survive. Half of all spontaneously aborted fetuses in the first trimester have major chromosomal abnormalities. Ten percent of couples who habitually abort have minor chromosomal abnormalities. 0.6% of babies have detectable chromosomal abnormalities, two-thirds of these being autosomal and one-third sex-chromosomal.

A biological marker is a biological characteristic or abnormality that may be associated with an abnormal gene or a gene close to (linked) to that gene. Use of biological markers allows a more direct search for a 'candidate' (for the disorder) gene. The researcher can focus on the genomic region, if known.

Unfortunately, some markers are state rather than trait markers, the latter being more informative.

Gregor Mendel⁸⁷³ worked out his Laws of Heredity by studying the results of crossing pea plant seeds, which can be smooth or wrinkled. He described the phenomenon of *independent assortment*: the pattern of inheritance for one trait was unaffected by the transmission of another trait. However, it has since been shown that when genes for two traits lie close to one another on a chromosome they do not obey Mendel's independent assortment, i.e. they demonstrate linkage.

*Recombination*⁸⁷⁴ (crossover) is a rearrangement of alleles due to crossovers, i.e. an exchange of genetic material between pairs of homologous chromosomes during meiosis. For example, Mr A got a copy of chromosome 12 from his mother (another the other copy from his father) which is a mix of her 2 copies of that chromosome, one of which came from her mother (the other from her father), and so on back through the generations. If the recombination fragment, a measure of the recombination event, is close to zero, *linkage* (inheritance of 2 or more markers as a single unit because of their close proximity on the chromosome and not because of chance) is likely. The ratio is expressed as its logarithm (ratio, i.e. between probability of there being linkage at a given recombination fragment and that of there being no measurable linkage), also known as the *lod score*. In other words, the lod score is the log of the odds on linkage in genetic research: the logarithm of the odds ratio. The *odds ratio* equals the odds of the observed pattern of co-segregation between marker and disorder occurring if the marker and disorder are linked divided by the odds of the same co-segregation occurring if the marker and disorder are not linked. Morton (1955) devised the lod score. A lod score of +3 or more carries a high chance of linkage (1,000 to 1 chance that co-segregation of DNA marker and disease did not occur simply by chance). Scores below -2 exclude linkage.

⁸⁶⁹ Duplication refers to the presence of 2 copies of part of a chromosome on the chromosome, e.g. involving part of chromosome 17 in the myopathy Charcot-Marie-Tooth disease.

⁸⁷⁰ Quiescent cells (G0 phase) are stimulated by growth factors like insulin-like growth factor via second messenger molecules. Transcription factors in the nucleus activate transcription factors and thence DNA synthesis. In G1 phase chromosomes are prepared for replication. In the S phase chromosomes are duplicated into chromatids. In the following G2 phase diploid cells divide into daughter phase. The cell then enters mitosis.

⁸⁷¹ Megakaryocytes are derived from megakaryoblasts by endomitotic reduplication, i.e. nucleus but not the cell divides (megakaryocytes therefore have many nuclei). Of course the cell then fragments into numerous platelets.

⁸⁷² The microtubule-organising centre (MTOC – tubulin-containing centrosomes) rearranges microtubules during interphase. This gives a structure on which daughter chromosomes separate. Paclitaxel, used to treat cancer, bind to microtubules and prevents movement of organelles. This action prevents formation of mitotic spindles and leads to death of the cell.

⁸⁷³ Augustinian monk.

⁸⁷⁴ Discovered by T H Morgan of Columbia University in fruit flies (*Drosophila melanogaster*).

Pardes ea,(1989) state that the risks for first-degree relatives developing a condition more often than controls are: bipolar affective disorder: 24 times higher; schizophrenia: 18; alcoholism: 10; and, panic disorder: 9.

The *pseudoautosomal region* of the sex chromosomes is a segment of sequence homology between the X and Y chromosomes in which meiotic cross-over (recombination) can occur. Depending on its exact location, a gene situated within this region could be inherited either in an autosomal or in a sex-linked manner. The process of inactivation of the X chromosome is complex. Normally, one X chromosome exists in an inactive, packaged state, formed during the late blastocyst stage: heterochromatic *Barr body*. The X inactivation centre is found at Xq13.3. There, an X inactive-specific-transcript produces an RNA called Xist that coats its own chromosome. This is followed by other chemical events that maintains the inactivated state. Some parts of the 'inactivated' X chromosome remain active, the so-called pseudoautosomal regions.

Epigenetics investigates heritable modifications of gene function, such as the expression of a gene via DNA methylation or changes in chromatin structure. Such changes are heritable but reversible. They can be caused by the environment during life and then be passed on to progeny. Such processes can change phenotypes and might explain why major psychiatric disorders do not follow the Laws on Mendel and they may explain how environmental factors translate into biology. Chromatin configuration can allow it to be activated (open; euchromatin - can be accessed by transcription factors) or inactivated (condensed; heterochromatin – cannot be accessed by transcription factors). Histone acetylation or methylation and DNA methylation influence transcriptional activity in various ways⁸⁷⁵. Some neuropsychiatric conditions seem to be caused by epigenetic changes, e.g. Rett syndrome and even some of the major 'function disorders' such as schizophrenia. Modern ideas of inheritance have been called '*hard inheritance*' (you transmit to offspring only those characteristics with which you were born – based on ideas of Sir Francis Galton [1822-1911] an English eugenicist and polymath and relative of Charles Darwin, and those of Friedrich Leopold August Weismann [1834-1914] a German biologist and evolutionary theorist). Jean-Baptiste Lamarck (1744-1829), a French biologist, believed that the genetic basis of characters could be changed by factors such as the environment or disuse. The modified genotype could then be transmitted to the next generation. A German-born biologist who died in the US, Ernst Mayr (1904-2005) coined the term '*soft inheritance*' to encompass Lamarckism and related ideas. Epigenetics, a modern concept, suggests that Lamarck may have not have been far wrong.

Modern psychiatric classifications involve tighter criteria than heretofore. They do not address the question of external validity or the likely clinical heterogeneity within a given diagnosis (e.g. PSE). Psychiatric disorders are probably heterogeneous, with different genetic and non-genetic mechanisms underlying different major genes, polygenetic forms, and environmental causes. The problem is made more complex by reduced penetrance and variable expressivity of the genotype. It may be that certain genes cause non-specific genetic predisposition to psychopathology, and that other genetic and non-genetic components are required to bring about a specific psychiatric disorder. Price, ea,(1987) suggested that many psychiatric 'illnesses', e.g. bipolar affective disorder and schizophrenia, may constitute a spectrum of disorders, rather than single entities; possible reasons include *nonallelic genetic heterogeneity* (genes interfere in developmental pathways at different points but ultimately lead to similar clinical manifestations) and *phenocopies* (non-genetic cases of an illness that present a clinical picture similar to that of a hereditary form, such as the possible roles for viruses or perinatal brain damage in schizophrenia). Assortive mating refers to the tendency of people with a mental disorder to mate with a person with a similar disorder. It is not uncommon in psychiatric hospitals. Assortive mating may confound linkage analysis (Q.V.) by increasing the extent of genetic heterogeneity within pedigrees: the person marrying into a family may introduce a genetic type of the disorder different from the one already segregating in the pedigree.(Baron ea, 1990)

⁸⁷⁵ Gene expression can also be controlled by RNAi (RNA interference) due to non-coding RNAs (e.g. siRNA [short interfering], shRNA [small hairpin], and mi RNA [micro])

Twin studies carry certain inherent difficulties. Monozygotic twins (MZ) derive from the division of one fertilised ovum and share an identical set of genes; monozygosity appears randomly⁸⁷⁶ in approximately 4/1,000 pregnancies. On average, dizygotic twins (DZ) have 50% of their genes in common, just like full siblings. MZ twins are always of the same sex, whereas DZ may or may not be. MZ twins, more than DZ twins or singletons, are more likely to have defects such as congenital heart disease, and obstetric problems are more common in twins, which might predispose to psychiatric disorder. Also, twins, especially if MZ (or DZ of the same sex), share intrauterine and rearing environments more than even other siblings. We will come across this issue again in other chapters, especially when discussing schizophrenia. The recurrence in families of DZ twins is common, but it is rare for MZ twins to recur in a family. One quarter of MZ twins have separate placentas.(Watson, 2004, p. 401) Also, the incidence of dizygosity varies in different populations, from about 3 to 40/1,000 pregnancies. According to some (Tsuang & Faraone, 1997; Riley ea, 2003, p. 254) but not all authorities (Löffler ea, 1994), twins *per se* are not at increased risk for schizophrenia. In fact, the 'typical schizophrenic is more likely than not to have no schizophrenic or schizotypal relatives'.(Tsuang & Faraone, 1997) Also, MZ are discordant for schizophrenia 50% of the time.

The Amish people, a small and isolated population with a small number of founders, are said to be prone to manic-depression: this group is likely to be genetically homogeneous, and the generality of the genetic findings to other populations remains to be determined (Egeland, ea, 1987). Baron, ea, (1987) reported tight linkage of affective illness to the classical X-chromosome markers, colour-blindness and G6PD deficiency, findings that strongly supported earlier suggestions that a gene on the X-chromosome is a causative factor in some cases of manic-depression. Many reports of linkage of psychiatric disorders to various chromosomes fail to be replicated, a fact that should temper enthusiasm for reported breakthroughs.(O'Donovan & McGuffin, 1991; Mendlewicz ea, 1991) The failure to replicate chromosomal findings in depression may not invalidate the original discoveries in 'isolated populations' like the Amish.(Weller, 1992) Price, ea(1987) wondered if major depressions with an age of onset greater than 30 years might be non-genetic, whereas cases of earlier onset may be familial and genetic. When genetic predisposition is worked out, prospective studies of at-risk individuals to identify specific non-genetic factors that contribute to the development of illness can be designed.

Terms

Aetiological heterogeneity: this may result from having both genetic and environmental causes.

Alleles: alternative forms, or versions, of the same gene, be they normal or abnormal.

Alternative splicing: the manner in which different protein isoforms can be produced. Different RNA species are produced by transcribing different exons (regions of coding). For example, if a gene contained 4 exons and if all 4 exons were transcribed one would be left with a large isoform. A smaller isoform are derived from a lesser number of transcribed exons. In other words, a given gene may yield a number of different proteins.

Aneuploidy: having an abnormal number of chromosomes. Aneuploidy may affect all cells or, as in mosaicism, some cells only, i.e. a mixture of normal and aneuploid cells as in some cases of Down's and Klinefelter's syndromes. Work is underway to non-invasively diagnose fetal aneuploidies before birth by analysis of free fetal DNA in maternal plasma.(Benachi & Costa, 2007; Dhallan ea, 2007; Driscoll & Gross, 2009)

Antisense oligonucleotide: piece of synthetic DNA with nucleotide sequence that is reverse of and complements part of messenger RNA.

Barr body: inactivated X-chromosome material produced by *lyonisation*⁸⁷⁷; the number of Barr bodies = the number of X-chromosomes minus one. They are usually detected on buccal smear. The gene for glucose-6-phosphate dehydrogenase (G6PD) is found at Xq28. G6PD deficiency occurs more often in males than females but, because of lyonisation, female heterozygotes may experience problems: because of random inactivation of X chromosomes there are two red cell populations, normal and G6PD deficient.

Candidate genes: genes encoding for neuroreceptors, enzymes involved in neurotransmission, or other proteins that might play a part in the pathogenesis of a disorder. Previous evidence suggests that such genes

⁸⁷⁶ Geneticists use the term *stochastic* which simply means a random event.

⁸⁷⁷ This is called after the English geneticist Dr Mary Frances Lyon who was born in 1925. Barr bodies get their name from the Canadian physician Murray Llewellyn Barr (1908-95).

may influence a phenotype. *Biological candidates* (e.g. a neurotransmitter) might be involved in biological or therapeutic aspects of the disorder of interest whereas *positional candidates* (e.g. disrupted in schizophrenia 1 on 1q) are chosen because of linkage or cytogenetic results suggesting a particular part (position) of the genome might harbour a susceptibility gene.

Anlage: primordium, inborn disposition.

Anticipation: a condition deteriorates clinically or manifests at an earlier age through successive generations, e.g. as happens in myotonic dystrophy and Huntington's disease (and debatably schizophrenia) due to triplet (trinucleotide) repeat expansion.

Anticodon: 3-base sequence in t (transfer) RNA molecule.

Autosomal dominant disorders: examples include achondroplasia, Huntington's disease (gene at 4p16.3), Marfan's syndrome, osteogenesis imperfecta, neurofibromatosis type 2⁸⁷⁸, and tuberous sclerosis⁸⁷⁹. In a normal gene, that repeats a sequence, CAG, the sequence repeat is 9-39, but in people with the Huntington's disease gene, the CAG repeat is 40 or more. Myotonic dystrophy is another example of a triplet (trinucleotide) expansion disorder. Trinucleotide repeat and age of onset are inversely correlated in Huntington's disease: the more repeats the earlier the onset. (Gusella & MacDonald, 1994)

Balanced translocation: a translocation without the presence of extra chromosomal material; persons with this type of translocation are called translocation carriers.

Bands: certain stains, such as Giemsa, reveal that chromosomes have a specific banding pattern that allows their identification. Chromosomes can also be identified by, for example, length and position of centromere.

Behavioural phenotype: The observed specific relationship between genotype of a syndrome and its behavioural or cognitive developmental profile and/or any specific association with comorbid psychiatric disorder. Examples include bipolar and schizophrenia-like states in the velocardiofacial syndrome, social anxiety in fragile X patients, and self-injury in Lesch-Nyhan syndrome.

Caenorhabditis elegans: A nematode worm with circa one hundred neurones. Presenilins code for a protein resembling G protein-coupled receptors and similar proteins are found in *C. elegans*. The latter proteins are involved in intracellular trafficking of proteins and may therefore be involved in apoptosis and β -amyloid protein processing.

Candidate loci or genes: association studies of disorders and genes (or loci) are more useful if there is reason to believe from prior evidence that the gene or locus is involved in a phenotype, i.e. is a candidate for, in the disorder. Positional candidate genes (e.g. dysbindin at 6p) are derived from linkage studies or cytogenetic research whereas biological candidate genes (receptors, transporters, or enzymes involved with a neurotransmitter) are chosen because they are thought to have a role in influencing the biological aspects of a condition or its treatment.

⁸⁷⁸ **Neurofibromatosis** consists of a number of related conditions. Skin pigmentation and tumour formation involving Schwann cells are found in these disorders. The two relatively common types are autosomal dominant conditions, often with fresh mutations. *Von Recklinghausen's disease* or *neurofibromatosis type 1 (NF1)* is the commonest type (NF1 mutation on chromosome 17 coding for neurofibromin). Most patients have low average IQs with some cases scoring above or below this. Performance IQ is particularly affected. Learning difficulties and ADHD may occur. Here one finds peripheral neurofibromas, café-au-lait spots, and pigmented hamartomata of the iris (Lish nodules). Large subcutaneous plexiform neurofibromata may deform parts of the body such as face or limb. Malignant transformation is possible. Blindness may occur in children with astrocytomas involving the visual pathways. Hydrocephalus may be due to stenosis of the aqueduct. A few patients develop seizures.

A variant involving non-germline mutation (i.e. a somatic mutation) is called Turcot's syndrome (brain tumour-polypoid syndrome 1).

Deletion of the region containing NF1 gene gives rise to a particularly severe form of the disease with intellectual disability.

In **NF2** there may be no skin lesions and bilateral acoustic schwannomas is the usual presentation. It is a multiple neoplasia syndrome due to mutations in NF2 tumour suppressor gene (22q). (Asthagiri et al, 2009)

⁸⁷⁹ **Tuberous sclerosis** (epiloia), affecting 1/6-10,000 of the population, is a multi-system, highly penetrant autosomal dominant disorder with hamartomata in many organs. The CNS shows abnormal neuronal and glial proliferation. It results from mutation of (at least) one of two genes on chromosomes 9 (TSC1 at 9q23, coding for hamartin) and 16 (TSC2 at 16p13.3, coding for tuberlin). Tuberlin and hamartin are associated with dysfunction neuronal and glial proliferation/differentiation. Affected people may have pitting of the teeth, seizures, skin problems (angiofibromata, ash leaf spots, shagreen patches, etc), tumours of the CNS (cortical tubers and subependymal nodules [+/- calcification] and giant cell astrocytoma), hamartomas of the retina, angiomyolipomata of the kidney, and rhabdomyomas of the heart. Neuropsychiatric problems include low IQ (65%), behaviour problems, autistic spectrum disorder, psychosis, and seizures (80% - most types of seizure are represented).

*Centimorgan (cM)*⁸⁸⁰: genetic distance in which the probability of a recombination between two loci occurring is 1%.

Centriole: one of the 2 poles of the spindle during metaphase.

Centromere: constricted chromosomal region including site of attachment to spindle; divides chromosome into 2, usually unequal, lengths or 'arms'.

Chromatid: at the end of interphase each chromosome has divided along its length into 2 daughter chromosomes, or chromatids; these remain attached to each other at the centromere.

Chromatin: basic unit of structure of chromosomes; irregular network of long coiled threads composed of DNA, histones and non-histone proteins.

Chromosome: one of a number of small bodies, found in pairs, into which the chromatin of a cell nucleus resolves itself before cell division; visible only during cell division, i.e. at prophase they become visible as discrete structures.

Codon: 3-base sequence in DNA molecule, each being decoded into one amino acid. An 'open reading frame' is a full set of codons lying between start and stop codons.

Coefficient of kinship: measure of expected proportion of genes in common between individuals: ½ for first-degree relatives, ¼ for second-degree relatives.

Deep resequencing: a method for sequencing a gene in thousands of subjects, usually employing high-throughput sequencing in order to increase speed and reduce cost.

Deletions: loss of whole or part of a chromosome; major deletions (partial monosomy) include Wolf-Hirschhorn (4p-) cri du chat (5p-); terminal deletions involve loss of the telomere; and interstitial deletion occurs within an arm of a chromosome.

Dichotomous trait: traits that can only be present or absent, with no 'shades of grey'.

Drumstick: lobular projection from nucleus of polymorphonuclear leucocytes in females. No relationship exists between number of X-chromosomes and number of drumsticks.

*Endophenotype*⁸⁸¹ (*intermediate phenotype*): a biological abnormality that seems to represent a more immediate result of the hypothesised genetic defect than does the clinical syndrome, e.g. panic following sodium lactate infusion in panic disorder, dysfunctional smooth-pursuit eye movement (Greenwood ea, 2007) or olfactory abnormality in schizophrenia (Turetsky ea, 2008), gating of the theta-alpha-frequency oscillatory signal in the paired-click paradigm in schizophrenia (Hong ea, 2008), deficient inhibitory control in ADHD (Goos ea, 2009), cognitive inflexibility in obsessive-compulsive disorder, or a small P300 amplitude in alcoholism. The usefulness of endophenotypes as a simpler path to the genetics of psychiatric disorders has been questioned. (Flint & Munafò, 2007) Also, biomarkers of incipient psychosis and schizophrenia may be unstable due to brain maturation (Pantelis ea, 2009) and longitudinal assessment may be needed to distinguish a normal from an abnormal trajectory of neurodevelopment.

Epistasis: 2 or more loci show a multiplicative interaction where the final result is greater than the sum of the effects of individual loci. This phenomenon may be important in interpreting genetic studies of families containing members with schizophrenia.

Exome: all expressed mRNA sequences in a given tissue.

Expressivity: variability in clinical manifestation of a genetic trait (see penetrance), e.g. neurofibromatosis may be expressed as anything from a visceral nodule to the Joseph Merrick syndrome ('elephant man').

Family studies: These can be of the family history variety where a history is taken from the proband, who may not be very knowledgeable, or the family study variety where all available relatives are directly interviewed.

F body: fluorescent body exhibited by males during interphase; consists of the Y-chromosome. Number of F bodies = the number of Y-chromosomes.

Fine mapping: precise mapping of a locus it has been identified by linkage (within megabases of DNA) or association (within tens of kilobases).

First-degree relatives: parents, siblings, children, all having 50% of the index person's genes; second-degree relatives are grandparents, grandchildren, aunts and uncles, all sharing an average of one-quarter of the index person's genes. (see coefficient of kinship)

⁸⁸⁰ This is a measure of 'genetic distance' between loci whereas 'physical distance' is measured in base pairs. 1 cM = 1 million base pairs.

⁸⁸¹ See complete issue of *Dialogues in Clinical Neuroscience* 2005; 7(2).

Flanking markers: 2 markers, one located on the telomeric side and the other on the centromeric side of a gene.

Genetic heterogeneity: this may be allelic when there are different alleles at the same locus, or nonallelic when there are defects at different loci.

Genetic marker: a 'tag' in close proximity to the chromosomal locus that actually expresses or causes disease.

Genetic probes: usually purified lengths of DNA or RNA specific for the particular gene or DNA segment suspected to be variant under study. In some conditions, such as sickle-cell anaemia, it is possible to detect the defective gene directly, without using a specific probe, by using one of the specific restriction enzymes⁸⁸² that reveal a pattern of DNA fragments unique to the mutation of interest. Some people affected by a disease or syndrome will have inherited the disease gene but will not have inherited the marker that is linked to it in the other family members. DNA markers can be used to detect carriers of abnormal alleles as early as the first trimester of pregnancy, using foetal DNA analysis.

Genome: the total DNA of a cell or organism; *genomics* is the study of genomes; the Human Genome Project refers to the co-ordinated international mapping of the genome. The mouse genome was thoroughly mapped before that of humans.

Germinal mutation: mutation in pre-gamete stage cell; can be inherited. (Cf. somatic m.) More than one-third of the human genome is expressed (turned on) primarily in the brain. (Sutcliffe ea, 1984) The genome is not simply the sum of individual genes; it is more like a recipe, variously influenced by individual ingredients. The notion of one gene for one protein is an oversimplification, many of them being capable of producing multiple proteins. The human genome contains about 25,000-30,000 (double that of the fruit fly) that are able to make at least a quarter of a million proteins! (Gribbin, 2002, p. 570)

*Heritability*⁸⁸³: a calculation of the contribution to causation made by genes in a population⁸⁸⁴; it is calculated from the known incidence of the condition in the general population and in relative, e.g. it has been calculated as being higher in schizophrenia (63-85%) than in congenital club foot (68%), anencephaly and spina bifida (60%), or congenital heart disease (35%). (Emery & Rimoim, 1990; McGuffin ea, 1995; Szmukler, 1998) Owen ea (2000) estimated heritability for schizophrenia (80%), bipolar disorder (80%), alcohol abuse/dependence (60%), major depression (40%), panic disorder (40%), phobia (35%), and generalised anxiety disorder (30%). Smoller ea (2008, p. 857) give the following approximate heritabilities: autism (90%), schizophrenia (70-80%), bipolar disorder (60-85%), ADHD (75%), late-onset Alzheimer's disease (60%), OCD (30-45%), major depression (40%), panic disorder (45%), alcohol dependence (35-60%), and phobic disorders (10-39%). One long-term follow-up of schizophrenic patients failed to find a history of the disorder in first- or second-degree relatives in 60% of cases. (Bleuler, 1978)

Hybridisation: single-stranded DNA immobilised on a membrane is probed with a DNA fragment complementary to that sought, so allowing its presence and size to be confirmed.

Homotypia: a tendency for a disorder to breed true within families. Early studies of schizophrenia supported this phenomenon, but more recent reports have been more equivocal. Also, the subtype of schizophrenia in an individual patient may change over time.

Hox (homeotic) genes: first discovered in flies but known to exist in humans, mutation in these genes cause conversion of one part of the body into another.

Hypervariable probes: those probes recognising several different alleles; therefore more likely to be highly informative since variation between individuals is high.

Imprinting: the foetus is able to tell the difference between maternally- and paternally-derived chromosomes; deletion of part of paternal 15q gives rise to the Prader Willi syndrome, whereas deletion of a similar region of the same chromosome from the mother causes Angelman syndrome. 'Imprinting' is also used to describe how newborn animals follow the first thing they see.

Informative family: one containing many affected members, the disorder running through one side (father or mother of proband) of the family only.

⁸⁸² Wener A D Nathans and Hamilton Smith received Nobel Prize in 1978 for discovery of restriction enzymes.

⁸⁸³ This statistic applies to populations and to not to individuals.

⁸⁸⁴ Heritability may vary with the population being studies. Also, as the population becomes more genetically homogeneous the apparent heritability of a trait decreases.

In-situ hybridization: technique using labelled DNA or RNA probes to hybridize to complementary RNA coding for a particular protein. Using autoradiographic methods, it is possible to quantitatively study gene expression in individual neurones.

Isochromosomes: rarely, the centromere (often of the X chromosome) divides horizontally instead of longitudinally leaving a chromosome consisting of either 2 long arms or 2 short arms.

Junk DNA: stretches of DNA separating genes; accounts for more than one-third of genome; of unknown function, but may be important, e.g. for evolution.

Karyotyping: chromosomes can only be viewed with clarity during cell division; phytohaemagglutinin is used to stimulate cell division in vitro, then colchicine is used to arrest cell division in metaphase; hypotonic saline is then used to swell the cell so as to separate the chromosomes from one another; stains, such as Giemsa, demonstrate the banding properties (light and dark bands that are characteristic of each chromosome⁸⁸⁵); a photograph is taken, from which the chromosomes are cut and arranged in homologous pairs. The term *karyotype analysis* simply refers to the visualisation of chromosome number and gross structure. *Fluorescent in-situ hybridization* (FISH) involves using fluorescent probes to investigate chromosomal or submicroscopic chromosomal changes, e.g. foetal cells may 2 or 3 intranuclear fluorescent patches indicating a disomy or trisomy chromosome 21, the latter indicating Down's syndrome.

Kilobase (Kb): 1,000 base pairs.

Ligase: an enzyme that allows separate DNA sequences to be joined together.

Linkage analysis: tests if observed co-occurrence of a disorder and a marker for a genetic locus within a given pedigree are compatible with that locus contributing to disease susceptibility. One can attempt to trace a gene from a protein or a protein from a gene, or look at candidate genes.(Q.V.)

Linkage disequilibrium: in meiosis, alleles in one generation tend to diminish in subsequent generations because of recombinations aimed at reshuffling of genes. However, for loci closely situated to one another, recombination is rare, and associations tend to persist for many generations.

Locus (loci): a specific site(s) on a chromosome.

Major histocompatibility complex (MHC): the HLA system consists of a series of closely linked genetic loci situated in the MHC on chromosome 6p. T cells use HLA antigens as recognition molecules. Various psychiatric 'HLA-associated diseases' have been described, e.g. schizophrenia (A28) and narcolepsy (DQB1-0602 and DQA1-0101). Multiple sclerosis may share certain HLA associations with narcolepsy (DR7, DR2).

Monogenic disorders: single gene disorders. These disorders have low population prevalences, which suggests that common diseases (>1% of the population) are likely to be polygenic, as are many traits that have been genetically studied, such as IQ, height, or skin colour.

Monosomy: loss of a whole autosome; probably incompatible with human survival.

Mosaicism (in Down's syndrome): occurs when non-disjunction takes place during any cell division after fertilisation; there are normal and trisomic cells in the same person; the effects on cognitive development are very variable.(Thapar et al, 1994)

Multifactorial characteristics: this should be contrasted with unifactorial disorders (Q.V.). Various contributions come from one or more genes and the environment. Liability must pass a certain threshold: population incidence represents the threshold for the general population. Familial incidence is the threshold for relatives of patients with multifactorial disorder. Familial incidence will be greater than population incidence. The curve of liability is shifted to the right. Examples include IQ, weight, height, blood pressure, skin colour, and possibly schizophrenia, cleft palate, and congenital heart disease. These often have a normal frequency distribution curve.

Mutagen: any agent increasing mutation (change) rate in DNA, such as radiation⁸⁸⁶, high parental age, or chemicals.

Northern blotting: RNA fragments are not cut by restriction enzymes in this technique; instead they are blotted as full-length mRNAs onto membranes.

Notation for gene locations: this is a shorthand way of describing the position of a gene in the genome. E.g. Xq27-28 means that the gene is on the X chromosome, on the long arm (p, short arm, from French for

⁸⁸⁵ Each band is assigned a number. The gene underlying cystic fibrosis (CFTR at 17q.21) is in band 21 of long arm of chromosome 17.

⁸⁸⁶ Hermann Müller received the Nobel Prize in 1946 for discoveries regarding mutations caused by X-rays.

small; q comes after p), and, numbered from the centromere, in segments 27 and 28. The astute observer will have noticed that the example given is that of the fragile site in the fragile X syndrome. A + or – sign before a symbol refer to the addition or absence of whole chromosomes (e.g. 47, XY, +21 = male with Down's syndrome), whereas the same signs after a symbol refers to only part of a chromosome (e.g. 46, XY, 5p- = male missing part of chromosome 5, i.e. cri du chat syndrome).

Nucleotide: e.g. the organic bases thymine and uracil + phosphate + 5-carbon sugar, repeated. Bases are the only source of variability within nucleic acids.

Oncogenes: DNA sequences homologous to oncogenic nucleic acid sequences of mammalian retroviruses. A retrovirus is one that is able to induce its host cell to use viral RNA as a model from which to construct DNA. This reverses the dogma 'DNA makes RNA'.

Pairwise concordance: the proportion of pairs of twins concordant for a particular trait. To be more exact: number of twin pairs in which both twins are affected by a condition divided by the total number of twins. (see probandwise c.)

Paracentric inversion: stretches of chromosomal material are inverted within the same chromosomal arm (e.g. in haemophilia).

Partial trisomy: a translocation occurs where a part of a chromosome becomes attached to a different one. If parents are phenotypically normal carriers of translocations are at risk for having a partial trisomy for the first mentioned chromosome, i.e. they carry 1 pair of a chromosome plus a piece of another similar chromosome; about 5% of cases of Down's syndrome are partial trisomy 21.

Penetrance: probability of a disease genotype resulting in abnormal phenotype. In other words, the proportion of heterozygotes who express (see expressivity) the gene in any degree (some authors see penetrance as an all or none phenomenon, and expressivity as a more variable phenomenon); penetrance is a product of the modifying influence of other genes and the environment; some cases of tuberous sclerosis, for example, have only sparse facial papules because of low penetrance.

Pericentric inversion: swapping of chromosomal material from one arm of a single chromosome with the other arm of the same chromosome.

Phenocopy: environment-induced disorder that resembles an inherited one, e.g. congenital deafness could be caused by rubella, radiation, drugs, or a rare recessive gene.

Phenotype: The outwardly observable trait (e.g. height) or laboratory finding (e.g. protein) that results from (is coded for by) the genotype. When people have 1 copy of a certain allele and share the same phenotype as do people with 2 copies of the same allele the allele is dominant for that trait. A recessive allele would need to occur twice in the same person (2 copies) to be expressed in the phenotype. Co-dominance refers to the situation where the person has 1 copy of the allele and a phenotype that is somewhere between (intermediate) those with 0 and 2 copies of the allele.

Philadelphia chromosome: acquired chromosomal abnormality involving a deleted chromosome 22, its long arm being translocated to another autosome, usually chromosome 9; associated with chronic myeloid leukaemia.

Pleiotropism (pleiotropic genes): a gene with more than one effect on the phenotype; several genes may contribute to one disorder, and a single gene may contribute to several disorders; many psychiatric disorders may be polygenic, the summation of a number of genes, each of small effect.

Polygenes (polygenic): a character that is determined by more than one gene; many genes of small effect acting in concert to produce a phenotype, e.g. schizophrenia. (Gill, 1988) McClellan ea (2007) suggest that schizophrenia is not due to multiple common polymorphisms acting together but rather that genetically highly heterogeneous with many rare, highly penetrant, often individual- or family-specific predisposing mutations (common disease-rare alleles hypothesis).

*Polymerase chain reaction*⁸⁸⁷ (*PCR*): method for amplifying a specific DNA region to allow its analysis; in principle, the reaction can be performed starting from a single DNA molecule. There are a number of types of PCR (differential display, quantitative, real-time). These have demonstrated downregulation of key oligodendrocyte and myelination genes (incl. transcription factors that regulate these genes) in bipolar and schizophrenic patients, (Thachev ea, 2003) pointing to an overlap between both conditions.

⁸⁸⁷ The American biochemist Arthur Kornberg (1918-2007) discovered DNA polymerase (Nobel Prize in Physiology or Medicine 1959 – shared with the American biochemist Severo Ochoa [b. 1944] who worked on RNA synthesis). PCR discovered by Kary Mullis in 1984 (Nobel Prize in Chemistry, 1993).

Polymorphic: the information coded by base pairs is not a continuous series of base sequences that give the code for proteins. 'Spacers' that are edited out when RNA is manufactured interrupt them. Hence RFLPs (Q.V.), or the variation in fragment length (polymorphism) produced by the spacers.

Polymorphic markers: markers recognising fragments of variable size; at least 2 alleles should be present in the population to be useful.

Polymorphism: more than one in a hundred of the general population over a number of generations contains a particular DNA variation resulting from a mutation.

Polymorphism information constant (PIC): figure indicating usefulness of a polymorphic DNA marker, e.g. a PIC of 0.45 means that the probe would be informative in 45% of families.

Polyploidy: a whole set of chromosomes gained; incompatible with human life.

Positional cloning: a set of techniques by means of which disease genes are identified through their position in the genome rather than through their function.

Presumed obligate carriers: non-affected relatives the gene or genes for a disorder, such as the mother of a patient with schizophrenia who, although not psychotic herself, has a parent or sibling with schizophrenia.

Proband: a sampled individual with a condition or trait; propositus if male, proposita if female.

Probandwise concordance: the proportion of co-twins concordant for a trait when ascertained through affected probands; or, number of affected co-twins of an affected proband divided by the total number of twins.

Promoter and enhancer regions: stretches of DNA around genes that prompt the gene to express or shut down; they can act as binding sites for transcription factors that have a role in determining in what tissue or at what time in life a gene is turned on or off.

Protein kinase: enzyme that transfers a phosphate radical to a protein.

Proteomics: the study of proteins at a functional level (McGuffin, 2002, p. 20) or the study of how abnormal genes lead to the production of dysfunctional proteins and the latter's abnormal interactions with other molecules. (Pennington ea, 2005) An example is the finding of excess clusterin, an extracellular chaperone that regulates formation and clearance of amyloid, in Alzheimer's disease. (Thambisetty ea, 2010)

Recessive trait: recessive traits manifest only in the homozygous state, where there is a double dose of mutant gene. Offspring are usually normal, as would have been most of their parents. The most likely relatives to be affected are siblings. It is very difficult to trace affected individuals in the family history. If 2 heterozygous parents produce children, there is a 1 in 4 chance of a child being affected: ¼ will be normal, ½ will be carriers or healthy heterozygotes, and ¼ will be affected. Consanguineous mating is more likely when dealing with rare recessive diseases. The chances of first cousins carrying the same recessive gene are 1:8. In practice, consanguineous matings lead to a slight increase in perinatal mortality rate, congenital abnormalities and learning disorder. The risk is greatly increased if there is a history of recessive disorder in the family. Examples of autosomal recessive disorders include oculocutaneous albinism (ocular albinism is X-linked), congenital goitrous cretinism, Crigler-Najjar syndrome, cystic fibrosis, Friedrich's ataxia, galactosaemia, Gaucher's disease, glycogen storage disease, Hurler's syndrome, Niemann-Pick disease, phenylketonuria, Tay-Sachs disease, and Wilson's disease.

Reciprocal translocation: mutual swapping of part of chromosome between autosomes or between autosomes and sex chromosomes – when this occurs in germ cells the result may be partial trisomies and monosomies; however, the balanced genetic rearrangement may continue on and not be manifest phenotypically unless a gene is disrupted.

Recombinant DNA: chemically synthesised DNA, DNA produced in a different species from the original one (usually a bacterium) or DNA formed by joining DNA from 2 or more different sources.

Recombinant DNA technology: genetic engineering.

Recurrence risk: the risk of a relative developing the same condition as an affected probands.

Recurrence risk ratio (λ_1): ratio of risk of a disorder in a first-degree relative of an affected person/prevalence in general population. When the base rate of a disorder is low a high relative risk is still compatible with a low absolute risk.

Restriction enzymes: derived from certain strains of bacteria, these are able to recognise specific DNA sequences as targets for cleavage. Each particular enzyme has a particular target or site of action. The enzyme cuts the DNA at every point where the specific site or DNA sequence appears.

Restriction-fragment-length polymorphisms (RFLPs): inherited differences in the length of DNA fragments (due to loss of an existing restriction site or the acquisition of a new site) generated with restriction enzymes (restriction endonuclease digestion due to variation in DNA sequence at enzyme recognition site); they can be millions of nucleotides away from the disease gene. Two types of bacterial enzymes are used. Firstly, restriction endonucleases recognise specific DNA sequences of restriction sites at which they bring about cleavage of the molecule and are able to cut out a fragment containing a particular gene. There are also reverse transcriptases that allow synthesis of DNA from mRNA (the reverse of usual), the DNA then being labelled with radioactive marker and the resultant probe being employed to find a section of DNA with the complementary base sequence, to which it will hybridise, i.e. stick. (Weatherall, 1991) Fragments can be recognised by their different mobilities on a Southern blot. (Cf. VNTRs) New technology have superseded the study of RFLPs, e.g. single nucleotide polymorphisms (SNPs or 'SNIPS': variations [polymorphisms] in single bases [nucleotides: A, C, T, or G] in the DNA sequence: Nangle et al, 2004)⁸⁸⁸ and 'CHIPS' (allowing scanning of all chromosomes for allelic variations – false positives may be a problem with this technique). The DNA sequence variation underlying the majority of RFLPs is the SNP.

Reverse transcriptase: an enzyme that copies viral RNA into DNA, the latter inserting itself into host cell nuclear DNA. Zidovudine (azidothymidine, AZT) inhibits reverse transcriptase.

Ring chromosomes: rare deletion of the 2 ends of a chromosome, the broken ends (telomeres) fusing to form a ring; usually loses some chromosomal material; commonly associated with intellectual disability.

Segregation analysis: compares observed frequency of a disorder in a pedigree (i.e. ancestors of individuals over at least 2 generations) with the pattern that would occur if a hypothesised mode of inheritance were true. This is mainly used for conditions where one gene accounts for much of the variance, which does not include most of the major psychiatric disorders.

Sequence motif: sequences of DNA whose function can be inferred because of their resemblance to sequences whose function has been determined biologically.

Sex-linked conditions: There are no proven examples of Y-linked single gene disorders in man. All known sex-linked conditions are due to genes on the X-chromosome, and these traits may be dominant or recessive. The affected male cannot transmit an X-linked trait to his sons, but all his daughters are affected. Affected females transmit the trait to 50% of offspring of either sex. X-linked recessive traits manifest only in homozygous females, but they always manifest in males, there being nothing on the Y-chromosome to modify the trait. Carriers are usually healthy. The family tree will be modified by the ability or inability of affected males to reproduce. X-linked traits are never transmitted from father to son. It is very rare for a female to exhibit an X-linked recessive trait if she has an abnormal chromosomal constitution (such as XO, Turner's syndrome), or if she is homozygous for the mutant gene (from both parents). If, in females, in most cells, the normal X-chromosome is inactivated, the result is a 'manifesting heterozygote'. X-linked recessive traits include Christmas disease, haemophilia, Hunter's syndrome, Lesch-Nyhan syndrome, and nephrogenic diabetes insipidus.

Short interfering RNA (siRNA): This is a class of double-stranded RNA, 20-25 nucleotides in length, that interferes with the expression of a specific gene.⁸⁸⁹

Single nucleotide polymorphisms: These SNPs or 'SNIPS' comprise variations [polymorphisms] in single bases [nucleotides] in the DNA sequence. The DNA sequence variation in most RFLPs (Q.V.) is an SNP.

Somatic mutation: mutation in post-gamete stage cell; cannot be inherited. (Cf. germinal m.)

Southern blotting: Named for E M Southern. DNA fragments provided by cloning or using restriction enzymes are separated using electrophoresis in a suitable gel (such as agarose) and then visualised by dyes or radiolabelling. The fragments are transferred and attached to a membrane for further examination.

Telomere: natural end of a chromosome. It contains no genes. A repeated sequence (TTAGGG) halts replication at this site. Telomeres become shortened with age⁸⁹⁰, and cigarette smoking and obesity (via

⁸⁸⁸ SNPs for corticotrophin releasing hormone receptor 1 may have a protective role in reducing severity of symptoms of depression in adulthood in people who were severely abused as children. (Bradley et al, 2008)

⁸⁸⁹ Other functions include viral antagonism and genomic chromatin shaping. Other names include 'silencing' or 'small interfering' RNA. siRNA was discovered in Norwich in England during work on post-transcriptional gene silencing in plants.

⁸⁹⁰ The DNA repeat sequences plus associated proteins cap the ends of chromosomes. Women generally have longer **telomeres**. A common research approach is to measure telomere length in leucocytes. Each cell division shortens the telomere (because DNA polymerase is unable to completely replicate the 3' end of linear DNA) and such shortening accelerates with disease (insulin resistance, diabetes, obesity, atherosclerosis, hypertension, cancers, cardiovascular disease, vascular dementia, and chronic and severe stress). Telomeric defects are known to be involved in some inherited disorders, including certain congenital aplastic anaemias.

oxidative stress) shorten telomeres. (Valdes et al, 2005) Stem cells have longer telomeres than do differentiated offspring and progeria have very short telomeres. Because of the protective presence of telomerase, a germ cell replicates with no telomeric shortening. Most somatic cells do not express telomerase. Reactivation of telomerase protects malignant cells.

Transcriptome: description of all DNA that is transcribed into (all types of) RNA.

Transgenic: transfer of genes from one organism to another. The transferred genes or transgenes may work normally in the recipient. The latter organism is said to be transgenic or transformed, e.g. transgenic mouse.

Translocation: part of one chromosome becomes attached to a different chromosome (or a different part of the original chromosome, or assumes a different orientation such as inversion), e.g. material from chromosome 21 being attached to chromosome 14 in Down's syndrome.

Transposons: genome regions that commonly change location.

Triplet (trinucleotide) repeats: these consist of 3 nucleotides consecutive repeated within a region of DNA, e.g. CCG, CCG, CCG. They are not uncommon in the genomes of humans and other species. In 1991, a new type of genetic mutation was discovered, a dynamic or expansion mutation, in which the number of triplets in a repeat increases and the length becomes unstable. Nearly 20 diseases, including Huntington's disease, 2 forms of fragile X syndrome, and myotonic dystrophy, have been linked to trinucleotide repeat expansions. Such repeats are unstable and lead to inheritance patterns at odds with traditional Mendelian genetics. Prediction of Huntington's disease may never be 100% accurate due to some cases having a borderline number of repeats, i.e. there is no absolute cut-off. (Hayden, 2000) Suggestions have been made that psychiatric disorders like schizophrenia (But see Fortune et al, 2003), bipolar disorder, and autism might be caused in this way. (Margolis et al, 1999)

Trisomy: addition of an extra chromosome – less severe defects than with monosomy. Trisomy 8 usually results in (usually male) foetal loss, but survival, when it happens, is associated with moderate intellectual disability. Patau's syndrome⁸⁹¹ is due to trisomy 13. Trisomy 16 correlates with age of the mother. Trisomy 18 (Edward's syndrome⁸⁹²) is nearly always lethal in infancy with less than 10% surviving for the first year. Trisomy 21 is associated with Down's syndrome.

Unifactorial (unigenetic) disorders: these are single gene disorders, (the autosomal dominant and recessive disorders and X-linked recessive disorders) the opposite of multifactorial characteristics (Q.V.).

Vector: a DNA sequence capable of self-replication independently of the DNA of the host cell (e.g. a bacterium or yeast) into which it has been inserted.

VNTRs (minisatellites): a different form of polymorphism to RFLPs. Variable number of tandem repeats (VNTRs) of a relatively short oligonucleotide sequence. Tend to cluster at ends of chromosomes. The differences in the number of short oligonucleotide sequences found between 2 adjacent restriction fragment sites cause the variation in length of the DNA restriction fragments in VNTRs. *Simple sequence repeat markers (microsatellites)* are similar to VNTRs except that they are abundant and evenly distributed across the human genome, consisting usually of 2-5 nucleotides (di-, tri-, tetra-, and pentanucleotides). Because of high inter-individual variability microsatellites are commonly used as markers for linkage analysis.

Western blotting: a mechanism for blotting proteins.

Xenotransplant: organ or tissue transplanted from one species of animal into another.

Mitochondrial chromosomes

Mitochondria, highly motile subcellular organelles that fuse and divide (Chan, 2007), contain their own chromosomes. (Behan & Farrell, 2005) Mitochondrial DNA is abbreviated as mtDNA. The mitochondrion and its genome are thought to be remnants of a free-living bacterium, probably a proteobacterium.

Telomerase repairs and extends telomeres. Statins and omega-3 fatty acids (Farzaneh-Far et al, 2010) hold promise in blunting the effects of telomere shortening, as may physical activity. The 2009 Nobel Prize for Physiology or Medicine went to Elizabeth Blackburn, Carol Greider and Jack Szostak in the US who identified yeast cells with mutations that shortened telomeres leading eventually to cessation of cell division. They created telomeric RNA mutations in *Tetrahymena*, a ciliate protozoan, which led to cellular senescence. Aging of human cells is delayed by functional telomerase, the DNA in telomerase attracting proteins that form a protective cap at the end of the telomere.

⁸⁹¹ **Patau's syndrome** is usually fatal in the first days/weeks of life, although a small minority of cases survive the first year. Features include severe mental retardation, microcephaly, holoprosencephaly, deafness, seizures, heart and kidney anomalies, cleft lip/palate, and omphalocele.

⁸⁹² **Edward's syndrome** is characterised by severe mental retardation, intrauterine growth retardation, CNS/heart/kidney anomalies, breathing/feeding problems, omphalocele, micrognathia, low-set ears, and 'rocker-bottom' feet.

Mitochondrial chromosomes are circular, densely packed with no introns, and contain genes that encode for proteins or RNA molecules involved in mitochondrial metabolism. However, most of the proteins involved in regulating transcription, translation, and replication mtDNA are encoded in the nuclear genome, the latter also encoding seventy subunits of the mitochondrial respiratory chain.⁸⁹³ Unlike nuclear chromosomes that present normally in 2 copies per cell at the most, thousands of copies of mitochondrial chromosomes are present in each cell. *Heteroplasmy* refers to the uncommon coexistence of more than one type of mtDNA in a single individual.⁸⁹⁴ Since sperm contain no or very few mitochondria, these mitochondria **derive from the mother**. Leber's optic atrophy, leading to blindness in young men, is inherited via mitochondrial genes. The latter condition will affect all the offspring of an affected woman but none of the children of an affected male. Other examples of mitochondrial chromosomal disorders are MELAS, myoclonic epilepsy with ragged-red fibres (MERRF), Pearson's syndrome (various blood, exocrine, GIT, endocrine, and renal problems), Leigh's syndrome (subacute necrotising encephalomyelopathy), Kearns-Sayre syndrome (ophthalmoplegia, deafness, intellectual disability, cerebellar ataxia and heart block), and familial bilateral striatal necrosis.

Ageing

One theory of ageing is that spontaneous or free radical-induced base pairs deletions from or mutations in mitochondrial DNA diminish respiratory ability. This is unlikely given the huge mitochondrial DNA capacity compared to the low observed frequency of such mutations, although it might be a factor if the repair and catabolic needs of the body reached a critical enough level.(Bittles, 1997)

The telomere helps chromosomes not to fray when they divide. Younger cells have longer telomeres than older ones: they become shorter with each cell division. In progeria telomeres are short from the beginning. The enzyme telomerase is present in sperm, ova and foetus, but not in adults. It can increase telomere length, e.g. in skin cells. One potential danger of using telomerase would be excessive cell division (cancer).

Counselling

Genetic counselling is the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing and transmitting it, and of the ways in which this may be prevented or ameliorated. The process is made difficult by a lack of a sufficient number of available generations, lack of post-mortem studies, early death of a parent, illegitimacy, mutations, and a relative lack of experience in assessing people for psychopathology before genetic testing.(Berrios ea, 1995; Dermaut & Van Broeckhoven, 2002) Age-related estimation of risks can be provided with the help of a life-table (Newcombe, 1981). Counselling for dementing disorders should probably be given in a medical genetics facility by a multidisciplinary team.(Dermaut & Van Broeckhoven, 2002)

Prediction

Although not as straightforward in practice as in theory, consent for testing should be freely given, informed, continuing and given by a person to be tested who is competent to do so, i.e. has capacity. The growth of un-regulated direct to consumer testing⁸⁹⁵ is worrying.(Lenzer & Brownlee, 2008; Anonymous, 2008) Presymptomatic or predictive testing (PT) must include adequate provision for pre- and post-test counselling as well as long term psychological support.(Farrer, 1987) Resources for counselling are not always adequate.(Green, 1994) Farmer and Owen (1996) found that most people who request PT for Huntington's disease did not proceed with testing after initial counselling. They also warn against pressuring a couple into terminating a pregnancy simply because they would have to look after a disabled individual. It is important to be sure that the patient understands the nature and implications of the test.(Green, 1994) Although it would be wrong to overestimate the negative consequences of such tests,(Bundey, 1997) the reader should note the following problems encountered during PT for Huntington's disease (Morris ea, 1989; Harper, 1993a,b; Scourfield ea, 1997; Hayden, 2000): referral without the permission of the individual or of at-risk relatives; referral of minors; requests from adoption societies; lack

⁸⁹³ It is thought that nuclear and mitochondrial genomic expression is highly coordinated.

⁸⁹⁴ **Heteroplasmy** helped to identify the last tsar of Russia's remains. Age of onset and clinical severity of *myoclonic epilepsy with ragged-red fibres* vary widely, even in the same nuclear family, mainly due to heteroplasmy: each sufferer inherits a different mixture of normal and mutated mitochondria from the mother.

⁸⁹⁵ The commercial field of 'molecular diagnostics'. The Human Genetics Commission in the UK published guidelines for direct-to-consumer genetic testing in August 2010 but these may lack teeth when dealing with an international industry.

of a clear family history of the disease; the patient being already clinically affected, or only equivocally affected, or the patient is in denial about the possibility of an untoward test result; affected relatives unknown to applicant; refusal by subject or relatives to donate blood sample; use of false names; refusal to allow GP access to result; and, result requested by insurance company.(see Greely, 2005) A young German teacher was refused a permanent job in 2003 on the grounds that relatives had Huntington's disease.(Burgermeister, 2003; see also Tuffs, 2005) A Canadian study (Bombard ea, 2009) found that a family history of Huntington's disease, rather than genetic test results, resulted in distressing discrimination for about 40% of respondents. The Minister for Health (Republic of Ireland) told the Dáil (Lower House of parliament) that the *Health Insurance (Amendment) Bill, 2000* retains prohibition on taking genetic testing into account when determining health insurance premiums.(Anonymous, 2000a) Britain applied a moratorium on such usage. The United Nations Educational, Scientific and Cultural Organization (UNESCO) released a set of rules governing the handling of human genetic data in July 2003 in the hope that governments would prevent third parties from misusing genes predisposing individuals to a given disease, although it appears to have left open the possibility of disclosure 'in the public interest'.(Bosch, 2003)

Apart from any religious consideration,(Crauford ea, 1989; Bloch ea, 1989) the fact that Huntington's disease is usually deferred until mature adulthood may make prenatal testing a problem for some.(Smurl & Weaver, 1987) According to Connor (1993), writing about Down's syndrome, about one in 12 people in Britain strongly oppose all forms of prenatal testing. The attitudes of those who may share ones genes must be considered,(Shaw, 1987) as must the possible adverse psychological reactions to testees to the results (Kessler, 1987) or the procedure.(Marteau, 1993; Statham & Green, 1993) Depression in applicants for PT should be treated if found.(Bundey, 1997) According to Marteau and Croyle (1998) the psychological impact of PT depends more on pretest expectations, mood, and social support than the results of the test itself. People may be less likely to take up offers of predictive testing if no treatment is available.(Hayden, 2000; Neumann ea, 2001) Americans say that they would be more likely to take a foolproof test for Alzheimer's disease than one with a 10% false result; those who would not have a test would, naturally, not like the idea of having to live with the result; and confidentiality is only a concern for about a third of people.(Neumann ea, 2001) Disclosure of APOE genotyping results to adult children of patients with Alzheimer's disease in the US did not result in 'significant short-term psychological risks' but pre-test distress predicted post-test distress (Green ea, 2009), and test-related distress was reduced by a finding of APOE ε4 negativity. Advance directives, time spent with the family, and settling of financial affairs would be important considerations should a test prove positive.

Genetic research may ways in which environmental manipulation might mitigate pathogenic endowment from our genes.(Kirley & Gill, 2003)

Human gene therapy

Gene therapy is a highly contentious undertaking,(Anonymous, 1991; Anonymous, 2000b) still in its infancy. Pyeritz (1990) pointed out that this would need to be attempted soon after conception. Somatic gene therapy involves the introduction and expression of recombinant genes in somatic cells for the purpose of treating a disease.(Leiden, 1995) Back in 1993, (Davies & Williamson, 1993) at Great Ormond Street in London, bone marrow⁸⁹⁶ was taken from a child with severe combined immunodeficiency due to absence of adenosine deaminase. The normal gene was put into the child's cells using disabled retrovirus. The cells were then put back into the circulating blood. American scientists used ooplasmic transfer to produce live offspring, i.e. they took some mitochondria from a donor's egg cell and injected them into the egg of an infertile woman with presumed mitochondrial defects, the egg then being fertilised in vitro. The main source of human embryonic stem cells (ESCs) are embryos not needed for in vitro fertilisation⁸⁹⁷. However ESCs were created in 2007 by reprogramming⁸⁹⁸ human skin cells⁸⁹⁹ to behave like ESCs, a

⁸⁹⁶ Some children who received their own marrow after it had been genetically engineered developed leukaemia-like conditions.

⁸⁹⁷ President George W Bush banned use of federal funds to support ESC research, but the ban was overturned by President Obama in 2009. This order does not allow funding to create new ESC lines because of the Dickey-Wicker amendment which prevents use of federal funds to create human embryos for research in which they are later destroyed, as occurs when ESCs are extracted.(Tanne, 2009)

⁸⁹⁸ Genes are inserted into cells using a virus.

⁸⁹⁹ Mouse skin cells had been reprogrammed in Kyoto in 2006.

process not without hazards⁹⁰⁰. Modified fibroblasts that produce nerve growth factor have been transplanted in human forebrain to ameliorate the cognitive effects of Alzheimer's disease.(Tuszynski ea, 2005) However, a more practical approach may be to develop NGF mimetic drugs. McGuffin (2003) does not believe that gene therapy is a viable treatment for schizophrenia because of delivery (to CNS) problems, multiple gene involvement, and so on, but there remains the possibility of better drug targeting.

Cloning

A clone is a colony of cells that originated from a single cell. The cloning of the sheep 'Dolly' in Scotland was announced in March 1997. A nucleus taken from a sheep's mammary gland and implanted into an unfertilised oocyte which has had its genome destroyed.⁹⁰¹ Cloning of rhesus monkeys followed in America, leading to presidential concerns about the cloning of human beings. Cloning of human embryos in order to produce tissues for transplant purposes was reported from America in November 2001.

President Obama stated in 2009 that human cloning would never be allowed.

Cloning in humans was thought to be prohibited in Britain under the *Human Fertilisation and Embryology Act 1990* but a November 2001 High Court ruling pointed out that such was not the case and led to a governmental reaction to ensure prohibitive legislation. However, in May 2005, the Law Lords ruled that such cloning was not prohibited, i.e. it allowed a family to create a 'saviour sibling' so that it could donate various tissues to save the life of a brother or sister.(see also Wilmut, 2004)

The British *Human Fertilisation and Embryology Act 2008* became active in 2009. It regulates assisted reproduction (*vide infra*) allows scientific investigation into treatments for conditions such as Parkinson's disease. Extracorporeal embryos are regulated as are human-admixed embryos (a mixture of human and animal genetic material that is used in stem cell research). Selection of offspring on the basis of sex is banned. Same-sexed parents are recognised as legal parents of children conceived via donated sperm, eggs or embryos. Embryos can be stored for up to 55 years in cases of premature infertility.

As Clare (2000, p. 118-9) points out, the cloned offspring has only one genetic parent.

In 2009 the Irish Medical Council (medicalcouncil.ie) stated that doctors should not create new forms of life solely for experimental purposes. Neither should they involve themselves in human reproductive cloning.

Assisted reproduction

Advances in this technology are beyond the way people normally think and feel about having a baby.

Sperm from an anonymous donor or an ovum from the mother's sibling may create problems of identification with the baby for the woman's spouse. Confusion and distress can be minimised by appropriate counselling.(Apfel & Handel, 1999)

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⁹⁰⁰ E.g. mutations. Peripheral stem cell transplantation often leads to delirium because of infection, metabolic perturbation, subdural or cerebral bleeding, or (rarely) Wernicke's encephalopathy. Severe marble bone disease (osteopetrosis), for example, has been treated with stem cell transplantation.

⁹⁰¹ Dolly, an arthritis victim, was put down in February 2003 after she developed pneumonia.

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10

Schizophrenia and other non-affective, non-organic psychoses

Brian O'Shea

Schizophrenias

'In real life we don't treat diagnoses, rather we treat symptoms'. (Murray, 2003a)

'Schizophrenia is a misconnection syndrome. "Cognitive dysmetria", or poor mental coordination, leads to perceptions and actions becoming disorganised and confused, which creates difficulty in distinguishing between the internal and external world'. (Andreasen, 2003)

'Like a sandcastle with the sides falling away'.⁹⁰² (Prof Elyn R Saks, 2009)

Definition

'In the 100 years that we have known the diagnosis of schizophrenia, its definition has swung between a biological illness, a psychological dysfunction, and a social construct'. (van Os & Kapur, 2009)

Schizophrenia⁹⁰³ refers to an incongruity of mental functions as when, for example, the expressed mood is not in keeping with the accompanying words or thoughts⁹⁰⁴. Areas affected areas include mood⁹⁰⁵, thinking or talking⁹⁰⁶, behaviour⁹⁰⁷, and social functioning⁹⁰⁸.

Schizophrenia (Andreasen, 1999):

A brain disease

Manifested as diseased mind

Symptoms and signs too diverse to localise the disorder to a single brain region

A disorder of neural connectivity⁹⁰⁹ (Symond ea, 2005) caused by multiple factors affecting brain development

Final common pathway is a misregulation of information processing in the brain⁹¹⁰

⁹⁰² Prof Saks is a law professor in Southern California who has schizophrenia controlled by clozapine. Here she is describing what it felt like when she was becoming psychotic.

⁹⁰³ According to Jablensky (2003, p. 203), the attributes that define schizophrenia are inferential and are highly dependent on the patient relating private mental activity, there being no 'test' for schizophrenia. The word *schizophrenia* comes from two Greek words meaning a disconnection or splitting of the psychic functions and has no connection, except in popular fiction, with the Jekyll and Hyde character, the latter being more likely a psychopath. Bleuler's 'schizophrenia' is reminiscent of Kraepelin's 'intrapyschic ataxia' (splitting/fragmentation of functions of the mind). According to ICD-10, *psychosis* 'simply indicates the presence of hallucinations, delusions, or a limited number of several abnormalities of behaviour, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behaviour'.

⁹⁰⁴ The person smiles or grins when relating to a personal disaster.

⁹⁰⁵ Incongruous or blunted (reduced intensity of emotional expression). Impaired facial expressiveness also occurs in depression. (Trémeau ea, 2005)

⁹⁰⁶ Thought disorder, including delusions and 'loosening of associations', i.e. the connections between phrases or thoughts are tenuous or lost.

⁹⁰⁷ Mannerisms, stereotypies, excitement, stupor, posturing, etc.

⁹⁰⁸ Including a tendency to drift down the social scale. Hindrance to social achievement starts long before the first admission. (Agerbo ea, 2004) **Empathy** includes emotional recognition, emotional perspective-taking, and affective responsiveness. People with schizophrenia have difficulties identifying emotions correctly, spontaneously simulating the emotional world of another person, and responding adequately in terms of their personal emotional experience. (Derntl ea, 2009)

⁹⁰⁹ 'A wiring problem'. Semaphorins are one of a family molecular cues (receptors) implicated in nervous system development, including guidance of axonal projections and neuronal migration. Plexins are semaphorins that act with neuropilins. A variant of the gene encoding plexin A2 (PLXNA2) may be associated with schizophrenia (Mah ea, 2006) and with anxiety. (Wray ea, 2007)

The degree of impairment is relatively stable after a long fulminant course, following which cognition may even improve⁹¹¹

Andreasen and colleagues (Fuller ea, 2003, p. 27-8):

(a) Synchrony: ‘the normal fluid processing of information required during thought and speech’

(b) Cognitive dysmetria: disturbed synchrony (disturbed fluid co-ordination of mental activity resulting from anatomical or functional misconnections arising during early development and manifested as the symptoms of schizophrenia)

Handicaps associated with schizophrenia (Wing and Brown, 1970)

Premorbid - pre-dating illness, e.g. deficient in skills, poor motor coordination in childhood (Schiffman ea, 2009)

Primary - positive or negative symptoms due to the illness

Secondary - from having an illness e.g. institutionalisation, demoralisation, and medication

Problems with the diagnosis

Diagnosis is not the strict equivalent of disorder and is subject to change over time in both directions

Longitudinal observation across episodes is required for validation

Major problem in defining limits of the disorder/s - where does schizophrenia end and something else start?

Inconstancy - patients’ symptoms change over time

Number of patients diagnosed with schizophrenia depends on classification system employed (Murray, 2002)

Bias – simply changing the ethnicity of vignette cases may change the given diagnosis (Kay & Tasman, 2006, p. 937)

Various attempts at average economic cost⁹¹²/year to society (see O’Shea, 1997; Carr ea, 2004)

1987 British estimate: £1,1670 (\$2,5000)/patient

Broadly defined conservative costing (direct and indirect) for schizophrenia in England of £2.6 billion in 1997

UK’s National Institute for Clinical Excellence (NICE, a NHS body – Hargreaves, 2003) estimated schizophrenia accounted for > 5% of NHS budget

Another estimate from early 1990s was \$20-30 billion in direct and indirect costs/year for all US schizophrenic patients

Tsuang (2003) - direct costs (amounting to 41% of total cost) were \$19 billion⁹¹³; indirect costs made up 59% of total cost

Knapp ea (2004 - systematic review of cost of schizophrenia): schizophrenia accounted for 1.5-3% of total national healthcare expenditures; one-third to two-thirds of these costs derived from hospitalisation, irrespective of communitisation level of national inpatient provision

Non-adherence to antipsychotic medication significantly increases the cost of treating schizophrenia (Knapp ea, 2004)

Clinical trial-based cost-effectiveness analyses of antipsychotic tend to be favourable to newer antipsychotics, but face a number of threats to validity (Polsky ea, 2006)

⁹¹⁰ She would later propose a ‘misconnection syndrome’ involving connections between cortex and cerebellum with mediation via the thalamus. (Mitelman ea, 2005)

⁹¹¹ Various extensions of this theory, such as abnormalities of corollary discharge and feed-forward (preparation of sensory cortex for sensations arising from intended thoughts and actions) mechanisms, have been put forward in an attempt to explain hallucinations, (Heinks-Maldonado ea, 2007) a disrupted sense of self and will, and delusions. Andreasen agrees with Bleuler that thought disorder is the primary defining feature of schizophrenia, rather than some positive symptoms (additions to behaviour and emotion) as delusions and hallucinations. However, it is probably unlikely that one unitary model (e.g. insensitivity to linguistic violations) is universally valid.

⁹¹² James Joyce spent a large proportion of his earnings on a forlorn attempt at finding a cure for his daughter Lucia (1907-1982), including having her treated by Carl Jung. He refused to accept the severity of her illness. She was eventually diagnosed with schizophrenia at the Burghholzi psychiatric clinic in Zurich and died at St Andrews Hospital, Northampton. She may have been the muse for her father’s *Finnegans Wake*.

⁹¹³ \$10 bn for inpatients, \$1 bn for outpatients, \$6 bn for nursing home/domiciliary care, and \$2 bn for the criminal justice system.

Conventional antipsychotics save on costs and are associated with a gain in QALYs⁹¹⁴ compared with atypical drugs; (Davies ea, 2007) RCT in 'routine clinical practice' where treating clinician chose drug treatment in advance.

Reduction in tardive dyskinesia with atypical antipsychotics may *not* be cost-effective.(Rosenheck, 2007)

The author admits that this is not the whole story.

Using Standard Cost of Illness procedures Behan ea (2008) estimate total cost (in millions) of schizophrenia in Ireland, subject to limitations posed by unavailable data, was €460.6 in 2006: direct cost of care €117.5; indirect costs €343 (of which €43.8 was borne by families); and lost productivity €277.

Early intervention in those at high risk of psychosis may reduce costs.(Valmaggia ea, 2009)

Early intervention for psychosis in London 'highly likely' to be cost-effective.(McCrone ea, 2010)

Epidemiology

Prevalence: Male prevalence arguably equals female prevalence (see below). The British Office of Population Censuses and Survey (OPCS) reported a prevalence of 'functional psychoses' of 0.4% in 1993. The one-year prevalence rate for schizophrenia is of the order of 2-5 cases/1,000 of the population/year.⁹¹⁵

Incidence: The incidence of schizophrenia is much higher in the unmarried of both sexes than in the married and is probably no higher in Ireland than elsewhere. The figures for schizophrenia vary widely depending on admission policies⁹¹⁶, diagnostic practices⁹¹⁷, and differing methods of case finding. Taking admission diagnoses made by inexperienced staff and lumping together anything half-resembling schizophrenia all too often represents official statistics⁹¹⁸. Studies showing a higher incidence among males may suffer from missing late-onset⁹¹⁹ female cases. In fact, US criteria held that schizophrenia could not start after 45 years of age. Females may outnumber males in the 20% of cases starting after 45. There is some indication that the risk to siblings for developing schizophrenia in the case of late-onset disorder may be less than for younger onset but higher than for the general population.

Average incidence of schizophrenia = 21.8/100,000/year (0.03% or 22 new cases/100,000/year) (Tsuang and Faraone (1997)

⁹¹⁴ Quality-adjusted life-years.

⁹¹⁵ The lifetime prevalence of DSM-III-R schizophrenia in one rural part of Ireland was estimated at 0.54% for men and 0.28% for women. The study in which these interesting if unexplained figures were reported (Kendler & Walsh, 1995) found no sex difference in age of onset. The same group later found no connection between age of onset and the risk for schizophrenia in relatives. Aleman ea (2003) conducted a meta-analysis of the literature and found that the incidence risk ratios for men to develop schizophrenia relative to women varied from 1.31 to 1.42 depending on what studies were included in the analysis; the sex difference was smaller in older (pre-1980) than in later studies; and they found no significant sex difference in reports from developing countries. The point prevalence (prevalence at a point in time) of broadly defined schizophrenia in inner London in 1991 was 5.1/1,000 of the population. Tsuang and Faraone (1997) give a prevalence range for schizophrenia of 0.6-17/1,000 people surveyed/year, most studies giving a range of 3-10/1,000. A generally agreed international figure is 0.5% or 1/1,000. According to Jeste and McClure (1997), the prevalence of schizophrenia is 7% in siblings and 3% in parents of probands with late-onset schizophrenia.

⁹¹⁶ Rendering studies alleging reduced incidence of schizophrenia based on reduced first admission rates difficult to interpret. A Finnish study (Salokangas ea, 2010) found that annual first admission rates (per 100,000) fell from 1980 to 1991 but increased slightly thereafter. They were higher using ICD-8 but lower with DSM-III-R or ICD-10. Bed number availability changes, admission policy, and diagnostic practice may explain most variation, and the authors wondered if increased use of illegal drugs and better treatment of depression might be reflected in the increased figures.

⁹¹⁷ The idea that the incidence of schizophrenia is the same around the world has been challenged. To some extent this depends on the diagnostic latitude employed. Earlier work tended to look for 'nuclear' (narrow) schizophrenia whereas 'broad' definitions yield greater differences between countries. The McGrath ea (2004) systematic review found up to fivefold differences internationally.

⁹¹⁸ Officially, 21% 19%, 20%, 19%, 20% and 20% of admissions to Irish psychiatric facilities in 1994/1995, 1999, 2001, 2002, 2004 and 2005 respectively suffered from 'schizophrenia'; 39% of inpatients attracted the same diagnosis during census day, 2001.(Daly & Walsh, 2002 – 38% in 2002) Admissions for schizophrenia to Irish psychiatric facilities in 2001 accounted for 9%, 20% and 23% of admissions to private, general hospital, and health board facilities respectively; the male rate for admission for schizophrenia per 100,000 (223.4) was higher than that for females (135.5).

⁹¹⁹ *Dementia tardiva*: later onset schizophrenia. Not surprisingly, a Danish study (Thorup ea, 2007) found that incidence rates for males significantly exceeded those for females in the age range 17-40 years but by the age of 72 years 1.59% and 1.17% of males and females respectively had developed schizophrenia.

*Morbid risk*⁹²⁰: Lifetime risk varies from 0.3 to 3.7%, a generally accepted figure being 1%. (Tsuang and Faraone, 1997) International consensus now accepts onset of schizophrenia even into old age. (Howard ea, 2000)

Social class and sex: Goldberg and Morrison (1963) found the social class distribution of the fathers of schizophrenics to be similar to the general population, i.e. schizophrenic offspring drift down the social ladder. Schizophrenia may not be directly caused by poverty but may lead to it⁹²¹. It may also delay presentation for treatment. (Mulvany ea, 2001) Upward paternal occupational mobility might place stresses on offspring with latent disposition to psychosis. (Mäkikirö ea, 1997) Youthful onset is associated with a disorganised mental state and failure to climb the social ladder, whereas later onset is more often equated with paranoid delusions and a decline in social status. Peak age of onset of schizophrenia is in the third decade⁹²²; onset is 3-5 years later in females than in males⁹²³. (but see Kendler & Walsh, 1995 above) This sex difference does not appear to be artifactual and may relate to difference in brain maturation, or the condition may be more obvious socially in males. Oestrogens might offer a mild protective role in females. Relapse is more likely when oestrogen levels are low: during or just before menstruation⁹²⁴, the puerperium, and after the menopause. The illness may be milder in women. Long-term treatment with conventional antipsychotic drugs in women produces better outcomes and, even when controlling for body weight, lower doses are needed than in males. Chronic exogenous oestrogen treatment reduces DA transmission in animals. Attempts to equate puberty with age of onset of symptoms have suffered from small numbers and possible recall bias. One group (Cohen ea, 1999) found the earlier was puberty (menarche) in females the later were onset of psychosis and first hospitalisation, with men showing a trend in the opposite direction.

According to Murray (2008) it is difficult to induce psychosis before puberty. He points to the use of ketamine in children and wonders why methylphenidate does not induce psychosis in ADHD.

Not all studies support an equal sex incidence of schizophrenia, e.g. an Irish rural catchment area study of DSM-IV first-episode psychosis reported a 7.5-fold lower incidence of schizophrenia⁹²⁵ among women than among men. (Scully ea, 2002) However the incidence rate was low and incomplete case ascertainment was a possibility. A retrospective Chinese study (Phillips ea, 2004) suggests schizophrenia is more prevalent in women than in men, a finding criticised on methodological grounds by Ran and Chen. (2004) A systematic review (McGrath ea, 2004) found a male to female ratio for schizophrenia of 1.4. Inner city areas may attract people who already have, or will later develop, schizophrenia.

*Aetiology*⁹²⁶

'It is likely that schizophrenia is the final common pathway for a group of disorders with a variety of etiologies, courses, and outcomes.' (APA, 2002)

Psychology: Millon and Davis (1996) disagree with lumping dissimilar patients under the rubric of schizophrenia. Instead they suggest, without much in the way of evidence, that schizophrenia represents an end stage in which certain symptoms are shared and which is reached by a gradual decompensation of personality.

⁹²⁰ Probability that individual develops a disorder by a given age.

⁹²¹ Nevertheless, social adversity may contribute to psychosis among migrants. (Vanheusden ea, 2008)

⁹²² In the twenties, although the median age has been reported as being 19 years in America.

⁹²³ Hare ea (2009) found that age at onset of psychotic symptoms in schizophrenia was a function of genes and the patient's sex.

⁹²⁴ Irregular and absent menstruation is common with typical antipsychotics and there are many case reports incriminating risperidone. Bergemann ea (2007) reported significant improvement in psychotic (but not depressive) symptoms in females with schizophrenia during the luteal phase. Also, in a randomised double-blind study, Kulkarni ea (2008) found that adjunctive transdermal oestrogen reduced positive symptoms and general psychopathological symptoms in women with schizophrenia.

⁹²⁵ And 6.6-fold lower incidence of bipolar disorder.

⁹²⁶ The term *psychosis* was introduced by Ernst von Feuchtersleben (1806-1849) of Vienna in 1845. A fundamental problem with all attempts at finding a cause or causes for schizophrenia arises from the strong likelihood that 'schizophrenia' represents a heterogeneous group of disorders. (O'Shea, 1997) Andreasen (1999) believes that schizophrenia is related to maturational or developmental brain processes, such as neurite formation, synaptogenesis, excessive neuronal pruning, (Siekmeier & Hoffman, 2002) or apoptosis (programmed cell death – different from necrosis); the cause occurs therefore between the start of neurone formation and migration (*circa* second trimester) on the one hand and young adult life on the other hand.

Stress: For many years it has been noted that remissions in schizophrenia are often terminated by changes in the patient's environment. Roughly, four times as many patients from high expressed emotion (EE, a measure of criticality, hostility, intrusiveness, and overinvolvement) homes as those from low EE homes relapse during the first nine months at home following discharge from hospital after treatment of an acute episode. Young, single men, who are living with parents, are at very high risk from this type of ambient tension⁹²⁷ (Vaughn and Leff, 1976).

Expressed emotion (EE)

High EE – intolerance, intrusiveness, use of inappropriate and/or inflexible strategies

Low EE – tolerance, respecting personal space, sensitivity to needs

Expressed emotion and relapse rates as percentages (after Vaughn and Leff, 1976)

Low EE, on medication – 12%

Low EE, no medication – 15%

High EE, < 35 hrs. face to face contact*, on medication – 15%

High EE, < 35 hrs. face to face contact, no medication – 42%

High EE, > 35 hrs. face to face contact, on medication – 53%

High EE, > 35 hrs. face to face contact, no medication – 92%

High EE, < 35 hrs. face to face contact = 28% of patients

High EE, > 35 hrs. face to face contact = 69% of patients

*Face to face contact with family in hours per week.

Parents of offspring with schizophrenia often show a pattern of chronic grief.(Davis & Schultz, 1998) What is considered high or low EE will vary with culture. Many families do offer low EE environments to patients. Measures of EE may be inferior to the *relatives' attribution of responsibility for symptoms*: low EE relatives may see than as beyond the patient's control, whereas high EE relatives may blame the patient. Parents of children and adolescents with schizophrenia may manifest less EE than parents of adult schizophrenics.(Asarnow ea, 1994) perhaps because the former more easily conceptualise their offspring as being ill. Some researchers have failed to find an influence for EE on relapse rates. (McCreadie and Phillips, 1988)

People with schizophrenia may do better if they live in suburbs, if they are of high socio-economic status⁹²⁸, allegedly if they live in rural developing countries (Mojtabai ea, 2001; Ran ea, 2001), or if they perceive their relatives in a positive light. Stress may, of course, come from outside the family (occupational, social, etc). Various coping mechanisms, such as problem solving, and the neuroleptics, may prevent the effects of stress reaching the non-specific symptomatic stage. A high ambient tension may keep the subject close to the threshold for relapse, so that minor stresses (including a rise in EE) may precipitate the return of florid symptoms. There is evidence of an increase in EE levels in the three weeks before the onset of an episode of schizophrenia. The better caretakers are able to cope the less disruptive are their charges. Antipsychotic drugs reduce relapse rates in the presence of high EE, but only relatively so. A higher frequency of independent life events is probably required to initiate relapse in adequately medicated patients. If relatives can be trained to recognise non-specific symptoms, medication dose could be increased pending consultation. Relapse rates may be reduced by educating the family about schizophrenia and by conducting group sessions for those involved in the care of patients in the community.(Pilling ea, 2002a) Family intervention are usually conducted in the home by two therapists working together over a period of months.(O'Shea, 1997)

Falloon, Leff and others (Falloon ea, 1984) have done valuable work in this area. Whilst it makes sense to concentrate on improving the interpersonal coping skills of individual patients, focusing on the family unit may improve results.

⁹²⁷ Adolescent and young adult first degree relatives of people with schizophrenia or schizoaffective disorder may show physical anhedonia, and difficulties with/lack of peer/sibling/opposite gender relationships.(Glatt ea, 2006)

⁹²⁸ Low socio-economic status in schizophrenia arises because of poor work performance of self and/or parents, the latter being more likely than the general population to have schizophrenia or subclinical illness (including cognitive dysfunction/schizotypal characteristics).

While research has tended to concentrate of the stresses inherent in family life for the schizophrenic member, a schizophrenia relative can be difficult to live with.(Tantam, 1991) Patients with schizophrenia may be impaired in their ability to cope with normal levels of negative affect.(Bellack ea, 1992) It is debatable whether parental EE is a trait or a reaction. Relatives may dislike the idea of EE because it smacks of blame. It is important to emphasise positive aspects of EE reduction rather than negative aspects of high EE. EE levels may fall when carers feel less burdened and when there is less contact with the patient⁹²⁹.(Sczufca & Kuipers, 1998)

Life events lead to stress, which in turn leads to *non-specific symptoms* like insomnia⁹³⁰, and thence to a relapse in the illness.

Life events

Probably non-specific

Determine if a patient will fall ill, but not the illness itself

High EE and relapse is not specific to schizophrenia - also associated with mood and eating disorders

Meaning of the life event to an individual (*contextual threat*) has a major role in determining how that person will react

Time of life when an event occurs can influence what follows, e.g. asthma or acting out in a child, alcohol misuse or migraine in a young adult, or depression and confusion in the elderly

The woman with schizophrenia who is pregnant (Abel, 2007, pp. 646-7)

Increased likelihood of unwanted, unwelcome or unplanned pregnancy or pregnancy by rape

Symptoms may remain the same or worsen

Delayed presentation (for most of organogenesis)

Reduced cognitive capacity to self-monitor, adhere with antenatal care, or recognise labour onset

Pregnancy causes increased plasma volume, decreased antipsychotic drug absorption from GIT and entry to CNS, together with increased renal clearance: reduced drug efficacy

Increased likelihood of amniotomy, artificially induced labour, assisted vaginal delivery, caesarean section

As with other psychiatric disorders, more stillbirths, malformed offspring, and infant mortality

Fetal exposure to antipsychotic drugs: icterus, under/overactivity, blocked intestine, poor feeding, unstable vasomotor system

Reduced likelihood of longterm care of offspring and fear of loss of child custody

Steinberg and Durell (1968) found the frequency of schizophrenia to be particularly high in the months following conscription into the army. In a prospective Danish study, Khashan ea (2008) found an association between death of a relative of the mother during the first trimester of pregnancy and risk of schizophrenia in the offspring.

Van Os (2002) suggests that reduced cortical volume in schizophrenia is due to reduced social interaction, a phenomenon reported in animals⁹³¹, but this type of hypothesis ignores direction of causation. Rijdsdijk ea (2005), on the other hand, found that whole brain volume in schizophrenia was of genetic origin, while the size of the lateral ventricles was related to individual specific environment.

Post-traumatic stress disorder appears to be common in patients with schizophrenia or other severe mental disorders, prevalences ranging from 3.8% to 43% (mostly 29%-43%) being reported (compared to 8%-12% in the general population).(Combs & Mueser, 2007)

Immigrants: These have been reported to have an increased risk for 'schizophrenia'.

Possible reasons for excess of schizophrenia in immigrants/ethnic minorities (O'Shea, 1997; Cantor-Graae ea, 2005; Fearon ea, 2006; Veling ea, 2008a; Weiser ea, 2008)

⁹²⁹ Carer burden in cases of schizophrenia may relate to factors in the patient (symptoms, male sex, unemployment, marital status), the carer (coping powers, contact with patient, being the parent), and the country (worse in Britain than in Germany).(Roick ea, 2007)

⁹³⁰ Secondary to physiological arousal. Slow habituation to arousal is associated with delusional thinking and hallucination proneness.(Allen ea, 2007)

⁹³¹ The magnitude changes are much greater in the latter reports.

Professional *bias* against certain cultures⁹³²
 Poor *matching* for age with native controls
 Use of *tools* that have *not been validated* cross-culturally
 Stress of immigration
 Disadvantaged status⁹³³
 Differences in culture and appearance⁹³⁴
 Infection (e.g. poliovirus)
 Obstetric complications
 Excess *cannabis* abuse
 Tendency of *pre-psychotic* people to emigrate
 Living in a neighbourhood where they comprise a small *minority*⁹³⁵
 Increased risk for *all psychoses*⁹³⁶

Putative antecedents of schizophrenia such as *psychotic-like experiences*⁹³⁷ may be more common among children of Afro-Caribbean origin in the UK than among their white peers. (Laurens ea, 2008) Rates of mental hospital admission for immigrants to England and Wales tend to be higher for females. Many authors point to lower admission rates for schizophrenia in the countries of origin, (e.g. Selten ea, 2005) but this is open to many interpretations, such as ‘the dysfunctional or sick emigrate’, (Patino ea, 2005) ‘emigration makes you sick’, or ‘host countries imagine you to be sick’. Some studies show an excess of schizophrenia in second-generation immigrants but not in the actual immigrants, although others show an excess in first- and second-generation immigrants and in nationals with a history of foreign residence, (see Cantor-Graae ea, 2003) but it is difficult to explain such findings. (Cantor-Graae & Pedersen, 2007) Also, immigrants may have a better prognosis than the indigenous population of the host country, (McKenzie ea, 1995) probably because the illnesses are precipitated by social adversity.

Cantor-Graae and Selten, (2005) in a meta-analysis of the literature, found a mean weighted relative risk for schizophrenia among first- and second- generation migrants of 2.7 and 4.5 respectively. The risk was increased if migrants came from developing countries or if they hailed from countries where most people are black. Coid ea (2008) conducted an inner-East London population-based 2-year epidemiological study of first-episode psychosis in people aged 18-64 years. Black and minority ethnic subgroups all had increased incidence of affective and non-affective psychoses compared to white British people. Only black Caribbean second-generation individuals had a significantly increased risk compared to first-generation counterparts. Asian women (but not men) of both first-generation and second-generation were at increased risk for psychoses compared to white British people. Morgan ea (2008) looked at first episode psychosis cases and community controls in two English cities over three years. Cases were more socially disadvantaged and isolated, even when they confined the sample to affective diagnosis, a short prodrome, and short duration of untreated psychosis. The greater the disadvantage the more likely was psychosis to occur. The authors found similar patterns in White British and Black Caribbean groups, although the latter were more disadvantaged.

Psychodynamics/family theories: Freud, in 1911, published his analysis of Daniel Schreber, the presiding judge of the Dresden appeal court. This analysis (based only on Schreber's autobiography and the report of a Dr Weber) led Freud to conjecture that Schreber was unable to accept that he was a homosexual. Instead,

⁹³² More likely to be detained, brought by police, given emergency injections, less likely to be diagnosed as depressed or given psychotherapy.

⁹³³ It is difficult to disentangle cause and effect when studying minority groups, psychosis, and perceived disadvantage. (Cooper ea, 2008)

⁹³⁴ Israeli study in which Ethiopian immigrants had highest risk of later schizophrenia. (Weiser ea, 2008)

⁹³⁵ These results from Holland (Veling ea, 2008a) might be due to lack of social support or greater discrimination.

⁹³⁶ According to Fearon ea, (2006) African-Caribbeans and Black Africans in England are at especially high risk for both schizophrenia and mania.

⁹³⁷ About 15% of the population report such experiences (delusions and hallucinations), although clinical psychosis is much less prevalent. The importance of such symptoms is the subject of debate and opinion varies from normal variant to psychosis precursor. Zammit ea (2009) found an association in 12-year-olds between having definite symptoms and maternal infection during pregnancy, maternal diabetes, need for resuscitation, and 5-minute Apgar score. Bartels-Velthuis ea (2010) found a 1-year prevalence of auditory vocal hallucinations in 7- and 8-year-olds of 9%; 15% of these were reported to suffer significantly and to behave problematically; rural children had a higher prevalence but urban children were more functionally impacted by the experience; and there was little evidence of a role for developmental variables.

according to Freud, the following subconscious changes occurred: 'I love him' - 'I hate him' - 'It is not I who hates him but he who hates me' - 'I am persecuted by him' (denial with projection). This Freud would state was the basis for paranoid thinking. It is now thought Schreber may have suffered from either paranoid schizophrenia or encephalitis lethargica. Melanie Klein believed schizophrenia was caused in infancy (paranoid-schizoid position). There was a failure to realise people could have a number of characteristics, such as 'good' and 'bad', simultaneously.

Fromm-Reichmann, another psychoanalyst, coined the term 'schizophrenogenic mother' in 1948. This concept has completely fallen from favour⁹³⁸. Egeland and Sroufe (1981) state that the schizophrenic mother may be unable to offer secure attachment for her child, with resultant poor bonding, social incompetence and problem solving difficulties in the offspring. It is difficult to explain this phenomenon but it needs to be addressed.(Wan ea, 2007) Nevertheless, the offspring of mothers with psychotic disorders are at increased risk of several adverse outcomes, including early death.(Suvisaari ea, 2008) An affirmative answer to a query about depressed mood during mid-gestation does not increase the risk for schizophrenia in offspring but it might add to the pathogenic effect of a positive family history of psychosis.(Mäki ea, 2010)

Lidz, from uncontrolled psychoanalytic studies of a few, wealthy, families of schizophrenic patients suggested there were two types of abnormal families: marital skew⁹³⁹ and marital schism⁹⁴⁰.

Bateson and his colleagues, in 1956, spoke of the double bind wherein overt instruction is contradicted by covert instruction; the child can only give ambiguous and meaningless responses.

Weiser ea (2008) looked at responses of male adolescents to questions posed by the Israeli Draft Board and found an increased risk for non-affective/schizophrenic psychoses in those people reporting poor family functioning. However, this project does not tell us anything about direction of causality.

Bebbington ea (2004) reported an excess of various forms of victimisation⁹⁴¹ in the past histories of adult psychotics in private British households.⁹⁴²

Social: In a follow-up study of first episode schizophrenics (FES), Johnstone, ea, (1986) found most patients were not in high face-to-face contact with other members of the family; many lived alone; and EE (overinvolvement, hypercritical) was a weak predictor of liability of relapse. A short duration of symptoms prior to admission and neuroleptic treatment were significant predictors of good outcome.

Classification of life events

Uncontrollable: apparently imposed on the subject and outside his control

Controllable/possibly-independent: within his control, not associated with culturally sanctioned behavior, not due to illness

Controllable/probably-dependent events: within his control, objective evidence suggests they might have been brought about by behavior regarded locally as abnormal and possibly arising from the early stages of mental illness

Doane ea (1986) reported that a behaviourally-oriented, problem-solving family approach may have decreased the risk of relapse in the first nine months after discharge from hospital by teaching families concrete ways of solving problems and concomitantly reducing the amount of negative emotional relating between family members.

Historically, urban life was often considered to protect against insanity.(e.g. Hood, 1862, p. 52) In a Nottingham study (Giggs & Cooper, 1987), people with schizophrenia showed the expected concentration in central city areas of low socio-economic status, whereas a more varied distribution was found for affective psychosis. It is probable that the former seek out the low levels of social demands for performance and the relative anonymity of city centres, whilst the latter benefit from periods of normality, the manic

⁹³⁸ That being said, the schizotypal mother-schizophrenic offspring is a not uncommon and difficult to manage clinical situation.

⁹³⁹ One parent dominant, usually the mother, and the other partner yields to her whims.

⁹⁴⁰ Parents hold contrary views, leaving the child with divided loyalties.

⁹⁴¹ Especially **child sexual abuse**. Shevlin ea (2007) found that physical abuse predicted psychosis, rape being particularly predictive in males. Fisher ea (2009) looked at gender differences in the association between childhood abuse and psychosis and found that **physical** (even more than sexual) **abuse** was important in females but found no association in men.

⁹⁴² These cases were not identified by standardised clinical interview, reporting bias may have contaminated the results, and controlling for depression 'somewhat reduced the odds ratios for the individual experiences'.

drive, or other unknown associated factors. Sundquist ea (2004) found in Sweden that the incidence of first admission psychosis and depression rose with increasing levels of urbanisation, although evidence from Denmark suggested that urban-rural differences in schizophrenia risk were unrelated to exposures that became more common in urban areas over time.(Pedersen, 2006) Murray (2003b) suggests that the increased risk for onset of schizophrenia in cities is due to social isolation. An association between vagrancy and schizophrenia has been noted in various parts of the world.(Harding, 1973) The ‘drift hypothesis’ holds that patients’ fortunes decline as a result of illness so that they fall down the social scale into poverty, whereas the ‘breeder’ hypothesis holds that impoverished city centres are aetiologically related to schizophrenia.⁹⁴³ There was a significant movement of patients with schizophrenia from outer to inner London during the period 1986-1991.(McNaught ea, 1997) Those inner London schizophrenics who were relatively mobile were more likely to be male, have prominent hallucinations, and have no general practitioner contact. Kelly ea (2009) found that the incidence of schizophrenia in males was higher in Irish urban than rural areas (incidence rate ratios [IRR] for males and females = 1.92 and 1.34 respectively) whereas the incidence of affective psychosis was lower in urban than rural areas for both sexes (IRR = 0.48 and 0.6). The drift-breeder controversy still attracts advocates to both sides of the divide.(O’Shea, 1997, 1998) One criticism of the breeder theory is that parents may have moved to cities because of their genetic predisposition to psychosis.

Reasons why cities might be inherently pathogenic

Complex⁹⁴⁴
 Viruses
 Malnutrition
 Stress⁹⁴⁵
 Noise⁹⁴⁶
 Drugs like cannabis⁹⁴⁷
 Head injury⁹⁴⁸
 Pollutants like lead

Downward social drift has also been demonstrated for bipolar disorder.(Tsuchiya ea, 2004)

Violence among schizophrenic patients

Violence by people who have schizophrenia may be slightly higher than in the general population but attracts a disproportionate level of media attention.(Dean ea, 2008, p. 540) Alcohol and substance abuse is a far greater cause of violence than mental illness.(Elbogen & Johnson, 2009) An actively psychotic patient who misuses drugs and who is not being followed up by mental health services obviously represents a greater threat than a patient whose illness is under reasonable control, whose progress is monitored, and whose habits are temperate.

⁹⁴³ Of course, both poverty and illness may lead to drift in that rented accommodation tends to be cheaper in less attractive, run-down areas, this being one factor in the genesis of ‘ghettoisation’.(Ramon, 2001)

⁹⁴⁴ Genetic predisposition → poor social and cognitive functioning → coping with urban life → increased risk of schizophrenia.(Weiser ea, 2007) Polanczyk ea (2010) followed up children from 5 to 12 years of age: self-reported hallucinations and delusions were familial and heritable and were associated with social risk factors such as urbanicity, domestic factors like maternal EE, behavioural/emotional/educational problems at age 5, and comorbidity, e.g. self-harm.

⁹⁴⁵ In the Schomerus ea (2008) study, 10% and 19% of patients with schizophrenia were victims of violent and non-violent crimes; patients felt safer in rural than in urban areas; being a victim of violence was most strongly associated with alcohol/substance abuse and with criminal arrests by the patients themselves; and not feeling safe most clearly correlated with poverty and experience of being a victim. In a one-year study, Ascher-Svanum ea (2010) looked at involvement in the US criminal justice system of people treated with antipsychotic drugs for schizophrenia and related disorders: 46% of 609 such people reported at least one criminal justice encounter (these were most likely to be substance users and relatively poorly adherent with medication); the 2 most common encounters were being victim of a crime (67%) and being on parole/probation (26%); such involvement is common and costly.

⁹⁴⁶ Prodromal schizophrenia-spectrum patients who are unmedicated extract message-like meaning from meaningless noise.(Hoffman ea, 2007)

⁹⁴⁷ Boydell ea (2006) found a greater increase in cannabis use in the year before presentation with schizophrenia compared to other psychiatric disorders in part of London.

⁹⁴⁸ Childhood head injury plus a strong familial predisposition to schizophrenia may be important.(AbdelMalik ea, 2003)

Violence and schizophrenia

Tends to involve a minority of patients⁹⁴⁹

Mostly petty

May be serious and bizarre

Classically aimed at relatives and occurs at home

5-10% of people awaiting trial for murder in Western prisons have schizophrenia (e.g. Erb ea, 2001)

5% of homicide perpetrators in England & Wales have a diagnosis of schizophrenia (Swinson ea, 2007)

Schizophrenia is 10 times more common in prisons than expected by chance (Mullen, 2006)

May be associated with command hallucinations (Q.V.), longer pre-treatment illness, affectively charged delusions, delusions of being poisoned, attempts to confirm delusions, personality disorder, and alcohol or drug abuse (e.g. Walsh E ea, 2002, Moran ea, 2003; Foley ea, 2005; Friedman, 2006)

Threats to kill may lead to homicide (Warren ea, 2008⁹⁵⁰)

Predictors of violence were childhood conduct problems, drug abuse, victimisation, economic deprivation, and living situation; negative symptoms predict less violence; antipsychotics may only help when violence is related to acute psychopathology (Swanson ea, 2008)

Violent male forensic patients with schizophrenia had lower IQ and higher psychopathy scores than non-violent male forensic patients with schizophrenia (Fullam & Dolan, 2008)

Mullen (2006) suggests that psychiatrists have tended to underestimate the connection between violence and schizophrenia in order to assure the public and because they often do not see such offenders⁹⁵¹.

However, medical staff may be victims of such violence.(Vevera ea, 2005) The addition of antisocial personality disorder (Joyal ea, 2004) may modify homicidal acts committed by schizophrenics in that they may be more likely to assault non-relatives, to have used alcohol, and to have been involved in a row with the victim prior to the incident. Attentional problems in childhood may play a role in later criminality,(Cannon ea, 2002) although its specificity to schizophrenia requires further elucidation.

According to Hodgins and Müller-Isberner,(2004) schizophrenic men who break the law demonstrate long-standing antisocial behaviour, at least from mid-adolescence. Late-onset schizophrenia may be much less likely to be associated with violence than when onset occurs at an earlier stage in development.

Documented increases in violent acts committed by schizophrenics may reflect a general increase in community violence,(Wallace ea, 2004) although Vevera ea (2005) found little increase in violence from 1949 to 2000.

Schizophrenic patients who abuse cocaine may have less negative symptoms but more anxiety and depression.(O'Shea & Stokes, 2000) Alcohol abuse may be a risk factor for depression in first-episode schizophrenia.(Roche ea, 2010) Delusions of vampirism⁹⁵² is a rare cause of violence in schizophrenia.(O'Shea, 2000a)

Violence may be associated with cortical thinning in the medial inferior frontal and lateral sensory and motor cortex, especially on the right side, and surrounding association areas.(Narayan ea, 2007)

⁹⁴⁹ Based on patient interviews, Swanson et al (2006) found that the 6-month prevalence of violence was 19.1% (3.6% serious violence). Positive symptoms (e.g. persecutory thinking) increased the likelihood of all degrees of violence, negative symptoms having the opposite effect. Drug abuse was associated with minor violence! Serious violence was associated with psychotic and depressive symptoms, conduct disorder as a child (Hodgins ea, 2008), and victimisation. Dean ea (2007) looked at first episode psychosis and found 40% were aggressive at first service contact (half of these were physically violent) – youth, Afro-Caribbean ethnicity and history of past violence each contributed; aggressiveness was associated with mania and individual manic symptoms (for whole sample and for schizophrenia) – violent aggressive patients differed from those who were non-violently aggressive by being male, of a lower social class, and having offended before. However, Large ea (2009) conducted a systematic review and meta-analysis and found that rates of homicide by schizophrenia patients correlated strongly with total homicide rates; a pooled proportion of 6.8% of all homicide offenders had a diagnosis of schizophrenia; and factors associated with homicide in schizophrenia were likely to be the same as those in non-schizophrenia homicide, e.g. social disadvantage, substance abuse, and access to weapons.

⁹⁵⁰ The Warren ea (2008) study was based on people who were *convicted* of such threats.

⁹⁵¹ Elsewhere, Mullen and Sullivan (2007, p. 483-4) say that while there is a connection between psychiatric disorder and violence the risk is not that high, the lifetime chance of someone with schizophrenia committing homicide being 0.05% (similar to the risk in young males).

⁹⁵² Drinking own or others' blood. For a discussion of vampirism see Jaffe and DiCataldo (1994), Kelly ea (1999) and O'Shea (2000a).

The gene coding for COMT⁹⁵³ is located within the small (about 35 genes) region on chromosome 22 that is deleted in velo-cardio-facial syndrome (VCFS). (Blackwood & Muir, 2004, p. 163, *vide infra*) Reduced ability to breakdown catecholamines has been suggested as a factor in violence in schizophrenia, homozygosity for the low-activity COMT allele being commoner in violent cases and homozygosity for the high-activity form of the enzyme being commoner in non-violent cases, (Lachman ea, 1998) although other authors have found no evidence for a major role for the COMT gene in schizophrenia. (Chen ea, 1999) According to Meltzer (2003) COMT polymorphism predicts cognition in schizophrenia: the more COMT there is the more is DA removed and the poorer is cognition. In a meta-analysis, Glatt ea (2003) found a small risk for schizophrenia to be associated with the Val158/108 polymorphism of the COMT gene, but others disagree. (Williams ea, 2005) Stefanis ea (2007) found that army induction increased stress levels and that this stress exacerbated psychosis levels, and carriers of the COMT Val158Met Val allele were more susceptible to the effects of stress on the psychosis outcome than those with the Met-Met genotype. Thaker ea (2004) found a significant diagnosis by genotype interaction in that schizophrenic patients with the Met-Met COMT genotype showed poor predictive pursuit⁹⁵⁴.

In a prospective, two-year community-based American study of schizophrenic patients atypical antipsychotic drugs⁹⁵⁵ significantly reduced violent behaviour relative to conventional medications. (Swanson ea, 2004) The authors suggest that better adherence to prescribed treatment explained this difference, and better adherence was associated with less psychotic symptoms, substance abuse, and adverse medication side effects. Krakowski ea (2006) found clozapine superior to olanzapine, the latter being superior to haloperidol, in reducing violence associated with schizophrenia and schizoaffective disorder. McCue ea (2006) found haloperidol, olanzapine, and risperidone superior to aripiprazole, quetiapine, and ziprasidone in the treatment of acute schizophrenia.

Fertility and mortality: All psychiatric disorders carry an increased risk of premature death, the highest risk, from natural and unnatural causes, being associated with substance abuse and eating disorders. (Harris & Barraclough, 1998) The risk of premature demise from unnatural causes is especially pronounced in the so-called functional disorders, particularly schizophrenia and major depression. (O'Shea ea, 1983) Deaths from natural causes are particularly common in organic mental disorders, intellectual disability, and epilepsy. A disturbing report from Sweden found that the number of people with schizophrenia whose bodies were not discovered for some time after death increased in keeping with the decline in bed availability during 1952-2005 in Malmo. (Nilsson & Lögdberg, 2008)

Among people with schizophrenia in rural China all-cause mortality and suicide rates were greater in males than in females in a 10-year cohort study; male gender, earlier age at onset, older present age, longer illness duration, physical illness, inability to work, and no history of treatment were independent predictors of increased mortality. (Ran ea, 2007)

People with schizophrenia have been reported to have a reduced life expectancy by about 20% (males > females: Brown S ea, 2000) and a reduced reproduction rate⁹⁵⁶. A Finnish study suggests that long-term antipsychotic treatment, especially clozapine⁹⁵⁷, is associated with lower mortality compared with the non-use of antipsychotics. (Tiihonen ea, 2009) Brown ea (2010) reported on the 25 year mortality of a community cohort with schizophrenia: mortality risk was 2 to 3 times that of the general population, mostly because of natural causes (unnatural deaths tended to occur during the first 5 years of the study), and the authors suggested that cardiovascular mortality may have increased compared to the general population. The steepest rise in cardiovascular mortality appeared to coincide with the introduction of the newer antipsychotic drugs although the authors felt unable to form any firm cause-effect conclusions from this observation.

However, schizophrenia seems to continue to occur at a similar rate to that in the past 50 years. Inbreeding does not seem to affect the incidence of schizophrenia. (Tsuang ea, 2002) Married status may delay onset of illness, especially in men. Alternatively, less vulnerable people marry and stave off breakdown for longer.

⁹⁵³ Catechol-O-methyltransferase (COMT) is an enzyme that catalyses catecholamine (including dopamine) in the brain. The gene (at 22q11) contains a functional polymorphism (Val^{108/158}Met) that affects enzyme activity.

⁹⁵⁴ Smooth pursuit eye movements based on internal representation of the target motion – unlike responses based on retinal motion processing.

⁹⁵⁵ Clozapine, risperidone, or olanzapine.

⁹⁵⁶ Although fertility may be improving and more cases are living freely outside institutions.

⁹⁵⁷ This study covered 1996-2006. Quetiapine was associated with the highest risk.

Never married persons of either sex are likely to be admitted earlier in life than those married. (Hart *et al.*, 2007) Schizophrenic males rarely marry and reproduce⁹⁵⁸ and affected females have decreased rates of marriage and fertility. (e.g. Howard *et al.*, 2002) Study of a Swedish birth cohort (MacCabe *et al.*, 2009) found that, relative to the general population, people with schizophrenia had less children and grandchildren (partly due to lower marriage rates), their unaffected siblings had no more children than the population norm, there was a trend for offspring of schizophrenia patients to have more children, and patients with affective psychosis and their relatives resembled the general population regarding fertility measures. It seems, therefore, that either environmental factors are aetiologically important or that new mutations keep it going. An alternative hypothesis is that schizophrenia confers a biological advantage on the sufferer, although the evidence for this is not strong (e.g. Masterson & O'Shea, 1984; Feeley & O'Shea, 2001; Goldacre *et al.*, 2005). Reduced fertility among Finnish schizophrenics is not compensated for by higher fertility among their siblings. (Haukka *et al.*, 2003) Many studies attest to the high frequency of cigarette smoking (and drug and alcohol abuse: McCreadie *et al.*, 2002a) among patients with schizophrenia. This is associated with increased lipid peroxidation in first-episode cases. (Scottish Schizophrenia Research Group, 2000) Cancer may be more common in schizophrenia than in the general population, mainly due to an excess of bronchogenic carcinoma. (Lichtermann *et al.*, 2001) Breast cancer may be less common in Israeli schizophrenic females and in women with other serious mental illnesses. (Bark *et al.*, 2008) Dalton *et al.* (2004) found no evidence for a reduced risk of cancer in parents of schizophrenic patients, a finding opposite to that of Levav *et al.* (2007) A large, 11-year, prospective study (n = 3,470) found that schizophrenic patients had a standardised mortality rate (SMR) 4 times that of the general population with cancer being the second most frequent cause (global SMR of 1.5); there was an increased mortality by cancer, especially from breast cancer in women and lung cancer in men; and baseline duration of smoking and age greater than 38 years predicted lung cancer death. (Tran *et al.*, 2009) Women with schizophrenia in Manitoba are less likely to get appropriate cervical cancer screening than are their peers⁹⁵⁹. (Martens *et al.*, 2009) Although schizophrenics may have less rheumatoid disease than the general population they are not immune from it. (e.g. Feeley & O'Shea, 2001) Indeed, there is Danish⁹⁶⁰ evidence that suggests that autoimmune disorders may be more common in schizophrenia sufferers than in the general population. (Eaton *et al.*, 2006) Chronic obstructive pulmonary disease is more common in people with serious mental illness than in the general population. (Himmelhoch *et al.*, 2004) Various authors have speculated about whether schizophrenia is becoming milder with a better prognosis. The apparent decline in the frequency of some subtypes, such as catatonia⁹⁶¹ (Cf later), has been noted with interest, although some authors contest the validity of this decline on methodological grounds.

⁹⁵⁸ Although they may have more children when they do marry than do married schizophrenic females.

⁹⁵⁹ The authors suggest that their finding suggest a need for greater involvement by primary care services.

⁹⁶⁰ The rarity of such disorders makes interpretation of the Danish data problematic.

⁹⁶¹ Catatonia was seen as a 'schizophrenic' issue only until recent times.



Catatonia

Season of birth: There is a reported excess⁹⁶² of schizophrenic births in winter and spring from the northern (O'Shea, 1997; Davies ea, 2003) but not the southern hemispheres,(McGrath & Welham, 1999) raising concerns of a possible viral aetiology and the possible role of obstetric problems.⁹⁶³ Season of birth effect is small, with differences of only 5-10% from expected rates. It may be important in some cases. O'Callaghan (1989) noted an excess of spring births in the general Irish population and he found that schizophrenics with a family history of schizophrenia followed the same pattern, but that schizophrenics with a negative family history had an excess of winter births. A survey of Norwegian psychiatric inpatients born from 1866 to 1939 revealed a striking excess of winter births, a tendency which was less marked in patients from the higher social classes.(Odegard, 1974) Retrospective Scottish work suggested a cold autumn might lead to the birth of people prone to developing schizophrenia during the following spring.(Kendell & Adams, 1991) Kirkpatrick ea (2002; Messias ea, 2004) found an association between summer births and deficit (negative symptom) schizophrenia⁹⁶⁴. Being born or reared in urban areas may add to the risk of viral infection *in utero*. Research on urban/rural place of birth, the relevance of being male/female, and the time of year when one is born is on-going.(O'Shea, 1997; Mortensen ea, 1999; Lundberg ea, 2009) Migration processes are a source of spurious findings in research into the relation between health and urban life.(Jablensky, 2003, p. 221) Boydell ea (2003) described a large increase in broadly- and narrowly-defined schizophrenia, mainly in younger people, in part of south-east London (Camberwell). The authors were unable to state if this increase was due to a migration effect. Finnish work on birth cohorts suggest a move from rural to urban births over time, but there are still clusters that suggest possible genetic isolation.(Haukka ea, 2001) Pedersen and Mortensen (2001) in Denmark found that the longer one lived in an urban area and the higher the degree of urbanisation the greater the risk of developing schizophrenia. Van Os ea (2003, 2004) found both level of urbanicity and familial liability independently and synergistically increased risk for psychotic disorder.

Genetics: Schizophrenia often runs in families, the risk increasing with the number of affected relatives⁹⁶⁵. Various figures have been published stating the risk for different relatives. If both parents have schizophrenia the risk for their child is about 45%, compared to 1% in the general population. If one parent has schizophrenia the risk is 13%.⁹⁶⁶ If a parent and a sibling have schizophrenia the risk is 16%. If a

⁹⁶² Compared with controls.

⁹⁶³ Of course, there are other possible explanations, such as whatever psychosocial factors drive procreation practices in parents.

⁹⁶⁴ Also, there is some evidence that the same seasonal factor/s may affect brain development and personality characteristics of the general population.(Kirkpatrick ea, 2008)

⁹⁶⁵ And with severity of illness in the proband.

⁹⁶⁶ Gottesman (1991) suggests that this relatively low risk reflects a milder form of parental illness, i.e. more severe illness may reduce the likely of parenthood in the first instance.

sibling has schizophrenia the risk is 9%. The risk for second-degree relatives is 3-4%. The genetic input is most likely polygenic⁹⁶⁷. There is no evidence for a single gene causing a large increase in risk. Various loci⁹⁶⁸ have been highlighted by research as possibly being important in schizophrenia.⁹⁶⁹ These results should be approached with caution until there is much more in the way of replication.(Harrison & Owen, 2003; Crow, 2008) Stefansson ea (2002) identified several markers in the neuroregulin 1 (NRG1)⁹⁷⁰ gene (8p) making up a core haplotype that showed a significant association (relative risk 2:1) with schizophrenia, and an almost identical pattern was found by the same group in a Scottish population.(Stefansson ea, 2003; Alaerts ea, 2009) While McGuffin (2003) was enthusiastic about neuroregulin 1, he was less enthused about dysbindin⁹⁷¹ (6p), G72 (13q32 – G72 is now known as DAOA, i.e. D-amino-acid oxidase activator⁹⁷²), proline hydroxylase (22q), and COMT (22q) as positional candidate

⁹⁶⁷ As in diabetes: additive effect of a number of minor genes, i.e. **quantitative trait loci** or **QTLs** (QTL = genomic region containing naturally occurring allelic variations affecting a quantitative phenotype). Linkage (detects linkage over fairly long distances) and association (requires that DNA marker be closely linked to disease gene) methods have been used to map human QTLs. Continuous outcome measures that are related to schizophrenia biologically (e.g. schizotypy) are another approach in QTL research.

⁹⁶⁸ At **chromosomes** 1p (Tamil Nadu, India: Holliday ea, 2009a), 1q (e.g. SELENBP1 [selenium-binding protein 1 at 1q21-q22 – involved in rapid cell outgrowth], RGS4 [regulator of G protein signalling at 1q23.3] and disrupted-in schizophrenia 1 [important for cognition and development of cortex] and translin-associated factor X alleles at 1q42: Cannon ea, 2005; NOS1AP or nitric oxide synthase 1 [neuronal] adaptor protein at 1q21-22: Wratten ea, 2009; NOS1 was found to be associated with clinically significant variation in cognition: Donohoe ea, 2009; 1q23-25 associated with negative symptoms in Taiwan: Holliday ea, 2009b), 2cen-q13 (MAL – myelin and lymphocyte protein, important for genesis and function of myelin), 2q (GAD1 or glutamate dehydrogenase 1 at 2q31.1 which has a role in cognition; MDH1 or malate dehydrogenase at 2q13.3, involved in regulating metabolism), 2q32.1 (Zinc Finger Protein gene [ZNF804A]: In Irish and German patients [Walters ea, 2010] this genotype was associated with differences in episodic and working memory that were not found in controls, and exclusion of patients with lower IQ strengthened association between schizophrenia and ZNF804A), 2p (deletions of neurexin 1 gene reported in autism and some families with schizophrenia; Rujescu ea [2008] report that such deletions confer risk for schizophrenia if they affect exons), 3p, 5p, 5q (e.g. for abstraction and mental flexibility: Almasy ea, 2008), 6p (DTNBP1 [dysbindin] at 6p22.3 with role in formation of lysosomes [Kircher ea, 2009]), 6q23 (AHI1 or Abelson helper integration site 1 [Ingason ea, 2010]), 7q (GRM3; MET [mesenchymal-epithelial transition factor] proto-oncogene variation at 7q31; Burdick ea, 2010), 8p (PP3CC or protein phosphatase 3 at 8p21.3, involved in calcium signaling; NRG1 or neuregulin at 8p21-p12 with role in neuroplasticity/ErbB signaling), 10q (HSPA12A or heat shock 70kDa protein 12A at 10q26.12, involved in nerve cell development and maturation; 10q22.3 in Taiwan: Holliday ea, 2009b), 11q, 12p (CACNA1C: rs1006737), 12q (DAAO), 13q (G72; HTR2A or 5-HT2A receptor at 13q14.1-q32), 14q (AKT1 or RAC-alpha serine/threonine-protein kinase at 14q32.32 with role in nerve cell survival), 15q (CHRNA7), 17q (17q21 in families of Central American/Mexican origin), 19q (MAG or myelin-associated glycoprotein at 19q13.1; Almasy ea, 2008; Francks ea, 2008 – SNP of familial schizophrenia and familial bipolar disorder show peak suggesting shared susceptibility locus on 19q13), 20p, 22q (APOL or apolipoprotein gene cluster at 22q13.1-q12.3 with role in metabolism of lipids/fatty acids; COMT or catecholamine methyltransferase at 22q11.21 that has a role in cognition; PRODH2 or proline dehydrogenase at 22q11.21 which is involved in apoptosis) and Xq (PLP1 or proteolipid protein 1 [Hakak ea, 2001] at Xq21.3-q22 with role in myelination) according to different sources. An excess of sex chromosome aneuploidies (such as XXY and XXX based on the observation that among patients with schizophrenia sib-pairs are more often of the same than of the opposite sex); a translocation involving chromosome 11 (a large Scottish family with almost half having mental disorder, including schizophrenia, show a balanced translocation between chromosomes 1 and 11[e.g. Millar ea, 2000]); various loci on chromosome 6 (e.g. 6p23); a modest effect for a vulnerability locus on chromosome 8p; linkage to 10q22.3; inheritance of susceptibility via the gene for the 5-HT2A receptor (or one in linkage disequilibrium with it) on chromosome 13 (however, the same variant allele is not confined to schizophrenia); linkage between failure to inhibit the P50 evoked potential (common in schizophrenics and their relatives: Louchart-de la Chapelle ea, 2005) and a dinucleotide polymorphism at chromosome 15q13-14 (same site as alpha-7-nicotine receptor), and a 'dementia praecox'-like picture in Irish patients with linkage to the 8p22-8p21 region. Gurling ea (2006) found evidence for a link between **pericentriolar material 1 protein** (PCM1 – involved in maintenance of centrosome integrity and regulation of microtubule cytoskeleton) gene on 8p22 and susceptibility to schizophrenia with orbitofrontal gray matter volume deficits. PCM1 forms a complex at the centrosome with disrupted-in-schizophrenia 1 [**DISC1** at 1q42.1] and Bardet-Biedl syndrome 4 protein [**BBS4**] which provides an essential cortical developmental pathway. Suppression of PCM1 during cerebral cortical development leads to defective neuronal migration. Such defects are phenocopied by suppression of DISC1 or BBS4 and made worse by suppression of DISC1 and BBS4.(Kamiya ea, 2008) DISC1 encodes a multifunctional scaffold protein involved in neurodevelopmental processes and has been implicated in the genesis of schizophrenia.(Schumacher ea, 2009) DISC1 variants affect the level of social anhedonia, i.e. they are important in determining our ability to enjoy social interaction.(Tomppa ea, 2009) McClellan ea (2007) argue for multiple rare highly penetrant mutations predisposing to schizophrenia.

⁹⁶⁹ For a recent review see Gill ea.(2010)

⁹⁷⁰ Neuroregulin is a protein involved in directing neural stem cells to become neurones or glia. The connection between schizophrenia and NRG1 may involve a cell adhesion function.(Kanakry ea, 2007)

⁹⁷¹ **Dysbindin** = *dystrobrevin-binding protein 1* (*DTNBP1*). It has also been implicated in bipolar disorder, especially when accompanied by psychosis. The gene is at 6p22.3.

⁹⁷² According to Williams ea (2006) variation at the DAOA/G30 locus (chromosome 13) is not so much associated with schizophrenia/psychosis but rather with mood disorder episodes in both bipolar disorder and schizophrenia. Mood incongruent psychotic features in bipolar patients may be linked to 13q21-33.(Goes ea, 2007) Soronen ea (2008) suggest that the DAOA (aka G72) gene may play a role in predisposition to mixed psychosis and mania and visuospatial problems. Opgen-Rhein ea (2008) reported a

genes in schizophrenia. However, Williams *et al.* (2004) using Cardiff and Dublin samples, produced evidence that variations in the dysbindin gene confers susceptibility to schizophrenia. Weickert *et al.* (2004) found dysbindin mRNA expression to be reduced in schizophrenia. Fanous *et al.* (2005) found that a haplotype for dysbindin may predispose to psychosis with high levels of negative symptoms. Kishimoto *et al.* (2008) found preliminary evidence that the dysbindin gene is associated with risk of metamphetamine psychosis.

Copy-number variants⁹⁷³ (CNVs) may have a role in schizophrenia. (Vrijenhoek *et al.*, 2008⁹⁷⁴; Kirov *et al.*, 2009⁹⁷⁵; Guilmatre *et al.*, 2009; Grozeva *et al.*, 2010)

Genetic input is likely a graded matter in the general population. Murray and Dean (2008, p. 289) suggest that liability to psychosis (like hypertension) is a continuous trait in the population with schizophrenic patients lying at one extreme of this continuum. Schizophrenia, like criminality (Mednick & Finello, 1983), may have a genetic input but environmental influences are also important (see van Os *et al.*, 2009). Up to one-third of schizophrenics have no known family history of schizophrenia.⁹⁷⁶ Also, schizophrenia may be associated with a far wider range of mental disorders than we have been apt to think,⁹⁷⁷ a fact that may influence studies of risk factors. (Mortensen *et al.*, 2010) Onstad *et al.* (1991) found that paranoid schizophrenics had a lower likelihood of having affected first-degree relatives than did other subtypes as well as having a lower concordance ratio between DZ and MZ twins. Nonfamilial cases may have an environmental aetiology because they were more likely to show cerebral abnormalities such as enlarged cerebral ventricles.⁹⁷⁸ Some authorities (e.g. McGuffin *et al.*, 1994) suggest that schizophrenia can be explained entirely by genes or that non-genetic phenocopies account for very few cases. Seven (58%) of 12 adopted MZ twins were concordant for schizophrenia⁹⁷⁹ in a systematic review of twin studies, a point against an aetiological role for shared environment in the genesis of the disorder. (Gottesman & Shields, 1982) A meta-analysis of 12 twin studies (Sullivan *et al.*, 2003) found the point estimate of heritability in liability to schizophrenia to be 81%⁹⁸⁰; there was evidence for environmental influences as well (joint estimate of 11%), but this work threw no light on the nature of such influences.

Crow (1990) favoured a 'continuum of psychosis' and suggested that we failed to genetically demarcate schizophrenia from affective disorder. Dalby *et al.* (1986) described a case of MZ twins in which one had manic-depressive psychosis and the other had schizophrenia. Other authors have also reported overlap between affective disorders and schizophrenia in the families of patients with schizophrenia. (O'Shea, 1997; Knowles, 2003) Kendler *et al.* (1998), working in Roscommon⁹⁸¹, found a familial tendency to develop a wide variety of psychotic syndromes rather than schizophrenia *per se*, but vulnerability to develop depressive and manic affective illness was found to be somewhat more specific.⁹⁸² McKenna (2007, p. 341) states that depression and elation in schizophrenia fails to reach the level of 'a full affective syndrome', i.e. low mood is not accompanied by biological and other accessory symptoms of major depression and mania is not accompanied by distractibility, overactivity, and overspending. However, there is evidence (Kasckow *et al.*, 2009) that adding citalopram to antipsychotic medication in schizophrenia patients with subsyndromal depression does seem to improve their social and mental functioning as well as their quality of life. Anglin *et al.* (2009) found that schizophrenia patients with a family history of affective illness performed relatively

significant effect of DAOA variation on risk for schizophrenia, and is also important in terms of neurocognitive function, e.g. semantic fluency. Overlap between schizophrenia and bipolar affective disorder may be linked to 2p11-q14. (Goes *et al.*, 2007)

⁹⁷³ **Copy number variation** (CNV) refers to a segment of DNA for which copy-number differences have been found by comparing at least two genomes. Humans (diploid) usually have 2 copies of each chromosomal region, one per chromosome. This may vary because of deletion or duplication.

⁹⁷⁴ Affected genes in this report, all important in nerve cell functioning, were MYT1L, CTNND2, NRXN1, and ASTN2.

⁹⁷⁵ Deletions at 22q11.2 and 17p12, the latter known to cause hereditary neuropathy with liability to pressure palsies.

⁹⁷⁶ It should be recalled that one-third of cases of haemophiliacs has no family history of the disorder, but that does not make it an acquired disorder.

⁹⁷⁷ Are haplotypes shared across disorders or is shared environment important?

⁹⁷⁸ One possible cause for such 'sporadic' cases is periventricular haemorrhage.

⁹⁷⁹ Not dissimilar to twins reared together.

⁹⁸⁰ Owen *et al.* (2000) estimated heritability for schizophrenia (80%), bipolar disorder (80%), alcohol abuse/dependence (60%), major depression (40%), panic disorder (40%), phobia (35%), and generalised anxiety disorder (30%).

⁹⁸¹ Irish county in Connaught.

⁹⁸² There were a number of problems with this study e.g. lack of consistency with the existence of discrete classes does not refute the existence of such classes.

well on measures of IQ and executive function, perhaps suggesting the existence of a distinct subgroup that is biologically nearer to severe affective disorder than to schizophrenia.

A very large (more than 2 million nuclear families) Swedish study (Lichtenstein *et al.*, 2009), using a multi-generation register the hospital discharge register, found evidence that schizophrenia and bipolar disorder partly share a common genetic aetiology – 63% of the co-morbidity between disorders was due to additive genetic effects common to these two conditions. This research shows that the first-degree relatives of probands with schizophrenia or bipolar disorder are at increased risk for both disorders, a slap in the face for Emil Kraepelin! (Owen & Craddock, 2009) Indeed, a meta-analysis of family studies of probands with schizophrenia and bipolar disorder found that they coaggregated in families. (Van Snellenberg & de Candia, 2009)

Population-based cohort study in Denmark (Gottesman *et al.*, 2010)

Both parents admitted to psychiatric facility with a diagnosis of scz: risk of scz in offspring = 27.3% (39.2% for scz-related disorders)

One parent admitted to psychiatric facility with a diagnosis of scz: risk of scz in offspring = 7%

No parent admitted to psychiatric facility with a diagnosis of scz: risk of scz in offspring = 0.86%

Both parents admitted to psychiatric facility with a diagnosis of BP: risk of BP in offspring = 24.9% (36% if UPD was included)

One parent admitted to psychiatric facility with a diagnosis of BP: risk of BP in offspring = 4.4%

No parent admitted to psychiatric facility with a diagnosis of BP: risk of BP in offspring = 0.48%

Risk of scz in offspring with 1 parent each with scz and BP = 15.6%

Risk of BP in offspring with 1 parent each with scz and BP = 11.7%

Maximal risks of having any psychiatric disorder in offspring of parents who both had scz = 67.5%

Maximal risks of having any psychiatric disorder in offspring of parents who both had BP = 44.2%

Note: scz = schizophrenia; BP = bipolar affective disorder; UPD = unipolar depressive disorder.

Niemi *et al.* (2004) followed up all women born between 1916 and 1948 and treated for schizophrenia spectrum disorders in Helsinki psychiatric hospitals and looked at their offspring born 1960-4 and at controls. The cumulative incidences of schizophrenia and schizophrenia spectrum disorders among the offspring were similar to those in first degree relatives of probands with schizophrenia and adoptees whose biological mothers had schizophrenia. Children of schizophrenic mothers were also at increased risk for non-psychotic disorders, especially mood and substance use disorders, and the fathers of these high risk offspring had increased rates of psychiatric disorders, especially alcohol and substance use disorders⁹⁸³.

Rüdin⁹⁸⁴ performed the first systematic family study of schizophrenia. This was published in 1916 and reported an increased rate of dementia praecox among siblings of probands over the general population. Shur (1982) did a retrospective study from the case notes (and item sheets filled out by psychiatrists dealing with the subjects) of hospitalised schizophrenics. Those with a family history of psychiatric disorders were significantly more likely to have been born in the UK and to have older mothers. Those with relatives with psychiatric diagnoses other than schizophrenia were significantly more likely to have been diagnosed as schizoaffective. The author wondered if there was a constitutional trait in the parents of those patients with a family history of psychiatric disorders delaying child bearing.

Family studies: Lifetime expectancy of an individual in the general population for schizophrenia is about 1% but far higher figures are reported among relatives of schizophrenics. If both parents are schizophrenic the chance of one of their children developing the illness is about 25%; if there is only one schizophrenic parent the risk falls to around 12%. Only 5-10% of schizophrenics have a schizophrenic parent. (O'Flynn *et al.*, 2003, p. 82)

⁹⁸³ A Norwegian comparison of patients with schizophrenia and bipolar spectrum disorder found that the former were more likely to use centrally stimulating substances and used one or more non-alcoholic drugs more often, whereas bipolar spectrum disorder patients drank more alcohol and had a higher frequency of single use of cannabis. (Ringen *et al.*, 2008)

⁹⁸⁴ Ernst Rüdin (1874-1952), pro-Nazi, co-worker of Kraepelin.

Twin studies: MZ twins carry a 30%-40% risk⁹⁸⁵; a singleton has a 10% risk.⁹⁸⁶ There is some evidence to suggest that the rate of first admission to hospital for schizophrenia may be higher in DZ than in MZ twins⁹⁸⁷. (Klänning, 1999) In a follow-up study comparing schizophrenic MZ twins with their never affected monozygotic co-twins, the offspring of both groups were equally likely to develop schizophrenia, with age-corrected risks of 16% and 16.8% respectively, suggesting the possibility of incomplete penetrance in non-affected twins. Birchwood ea(1988) suggest that the majority of unaffected members of discordant schizophrenic MZ twin-pairs have abnormal personalities. Critics point out that twins share an intrauterine environment and may share perinatal hazards. Davis ea (1995) reported that MZ twins sharing a single chorionic sac (monozygotic) are more often concordant for schizophrenia than are dizygotic twins. Gottesman and Bertelsen (1989), among others, studied offspring of discordant MZ twins (only one had the illness) and found that the risk to children of the healthy twin was the same as that for the children of the affected twin, others putting the risk even higher. This suggests that the genotype for schizophrenia may remain unexpressed. The reason for this is not known. (See also Gottesman & Shields, 1982) Essentially similar findings have been reported for bipolar disorder. (Jones ea, 2002)

Adoption studies: A child of biological parents with schizophrenia adopted at birth by normal adoptive parents still retains more or less the same risk for the illness. If schizophrenic adoptive parents adopt the child of non-schizophrenic biological parents he carries the same risk for schizophrenia as anyone else (1%). Critics suggest that adoption agencies seek adoptive families resembling families of origin. The type of rearing a person genetically at risk receives in the adoptive home has a bearing on the likelihood of expression of schizophrenia spectrum disorder. (Tienari ea, 2004; Wahlberg ea, 2004)

*Pooled DNA and SNPs*⁹⁸⁸: In order to reduce cost, pooling of DNA has been used in a genome-wide study of schizophrenia in Cardiff.⁹⁸⁹ (Kirov ea, 2008) The Kirov ea (2008) study suggested that the SNPs rs11064768 (within a coiled-coil domain gene CCD C6O) and rs893703 (within a candidate gene for schizophrenia RBP1) may be important. However, Sanders ea (2008) carried out a large genetic association study of SNPs in 14 schizophrenia candidate genes and were unable to show that they accounted for a substantial proportion of genetic risk for schizophrenia, although small effects could not be ruled out. A meta-analysis of 32 genome-wide linkage studies of schizophrenia (Ng ea, 2008) suggested that future work might concentrate on chromosomes 1, 2q, 3q, 4q, 5q, 8p, and 10q. Large scale studies using big patient numbers are needed to further our knowledge and this necessitates the combined efforts of many investigators. (Owen ea, 2010)

Chromosome studies are popular but have yet to pay major dividends. Narrowly defined schizophrenia with a constellation of physical abnormalities, and a piece of chromosome 5 on chromosome 1, thus giving a partial trisomy of chromosome 5, has been reported. (Sherrington ea, 1988) Crow's (1988) so-called *pseudoautosomal theory*, wherein he locates the genetic mechanism for psychoses at the tips of the short arms of the sex chromosomes, has been influential. Crow (2002, 2008) states that language is a human facility made possible by lateralisation, in turn made possible by material from the X-chromosome moving to the Y-chromosome (recombination during male meiosis) and thus escaping inactivation: attention has been focussed on the region of X-Y homology and specifically one gene, protocadherin XY,⁹⁹⁰ which Crow suggests explains, at least to some extent, both language and psychosis⁹⁹¹. However, (Weinberger & Marengo, 2003, p. 335-6) most morphometric work has reported bilateral alterations, anatomical asymmetries are found in other primates, and Crow fails to address the more generalised deficits found in schizophrenia. Nevertheless, there is fMRI evidence to suggest that increased language activity of the right

⁹⁸⁵ Figures vary, e.g. some sources give lifetime expectancies of 46% for a MZ twin where the co-twin already has schizophrenia or, for a singleton, if both parents have the disorder.

⁹⁸⁶ Twins in general are probably no more likely to develop schizophrenia than members of the general population.

⁹⁸⁷ Although this must be interpreted with caution for methodological reasons such as the use of registers, mailed questionnaires, and the attendant risk of misclassification.

⁹⁸⁸ Single nucleotide polymorphisms (SNPs or 'SNIPS': variations or polymorphisms in single bases/nucleotides in the DNA sequence.

⁹⁸⁹ 3 pools were used: unaffected controls, schizophrenic patients, and patients' parents. Highest ranked SNPs were individually genotyped.

⁹⁹⁰ Protocadherin is a cell adhesion molecule involved in axonal guidance.

⁹⁹¹ Burns (2006) suggests that schizophrenia is by-product of social brain evolution in humans, with problems in the 'social brain', i.e. frontotemporal and frontoparietal networks. So-called 'mirror neurones' in this part of the brain help us to read the intended actions of others. He suggests that the basic problem in schizophrenia relates to a sense of detachment and disembodiment from the social self and social world. This concept receives support from the work of Schürmann ea (2007) with twins discordant for schizophrenia.

hemisphere may play a role in precipitating psychosis.(Sommer ea, 2004) Also, Somers ea (2008) found that non-right-handed people have higher schizotypy that reflects a higher incidence of bilateral language lateralisation, potentially underlying loosening of associations; the authors suggest that decreased lateralisation is a vulnerability model for schizophrenia spectrum features.

Nicotine (incl. smoking) in schizophrenia

Transiently normalises the P50 deficit.

Nicotine receptor may regulate sensory gating⁹⁹² (Leonard ea, 2002)

More specifically, the alpha 7-nicotinic receptor gene may be involved in auditory sensory gating defect reported in schizophrenics⁹⁹³ (Freedman ea, 1997) – linkage of impaired P50 inhibition was reported to a locus adjacent to the alpha 7-nicotinic receptor gene on 15q

Do schizophrenic patients smoke to improve filtering of environmental stimuli?

fMRI work is consistent with nicotinic receptor mediation of neuronal dysfunction in schizophrenia (Tregellas ea, 2005; Tregellas ea, 2009a)

According to Sacco ea, (2005) cigarette smoking may improve visuospatial working memory and attention in schizophrenic patients, perhaps via nicotinic receptors

There is some evidence that ondansetron, a 5-HT₃ antagonist⁹⁹⁴, improves P50 auditory gating in medicated schizophrenia patients (Adler ea, 2005)⁹⁹⁵

George ea (2003, p. 87) suggest that schizophrenic subjects smoke tobacco in order to improve their cognitive functioning, although Netski ea (2003, p. 168) suggest that they abuse whatever is available and that data do not support the self-treatment hypothesis

Nevertheless, there is some evidence that DMXB-A⁹⁹⁶, a partial alpha 7-nicotinic agonist improves cognition in people with schizophrenia (Olincy ea, 2006; Freedman ea, 2008)

Nicotine replacement therapy plus motivational interviewing/CBT may have utility.(Baker ea, 2006)

Nicotine, in mice, may upregulate glutamic acid decarboxylase 67 (GAD₆₇) expression by activating nicotinic cholinergic receptors located on cortical or hippocampal GABAergic interneurons.(Satta ea, 2008)

DeLisi ea (2002) suggested that failure to consistently replicate linkage reports might reflect an epigenetic mechanism (gene expression) rather than an effect of sequence variation.(see also Crow, 2007)

The *velo-cardio-facial syndrome* (VCFS)⁹⁹⁷ is due to small hemizygous chromosomal deletions in chromosome 22q11.2. Although the sample size may have been inadequate, according to Ivanov ea (2003) the rate of VCFS in patients with psychosis without learning difficulties may be as low as 0.6%. There are cleft lip/palate, congenital heart defects, thymic dysplasia, hypocalcaemia, nasal speech, intellectual disability (in almost half – of various degrees of severity), long facies, bullous nasal tip, and an increased incidence of schizophrenia-like⁹⁹⁸ and bipolar disorder-like disorders. However, Baker and Skuse (2005) looked at adolescents and adults with the syndrome and found an excess of psychiatric morbidity⁹⁹⁹, i.e. there is a continuum of developmental disruption followed by a decline in mental health in early adulthood.

⁹⁹² Sensory gating = ability to ignore unimportant environmental stimuli.

⁹⁹³ Decreased muscarinic cholinergic receptors, specifically M1 and M4, have been reported in prefrontal cortex (Crook ea, 2001) and M1 in the caudate-putamen in schizophrenia.(Dean ea, 1996)

⁹⁹⁴ 5-HT, 5-hydroxytryptamine, serotonin.

⁹⁹⁵ The notion of a defective **filtering of environmental stimuli** goes back to **Broadbent**.(1958) Hemsley (1977) applied defective selective attention theory to negative symptoms – patients learn to cope with information overload by slowed thinking, poverty of speech and flat affect, apathy and withdrawal. However McKenna (2007, p. 192) suggests that disordered attention may be more reminiscent of mania than of schizophrenia.

⁹⁹⁶ 3-[(2,4-dimethoxy) benzylidene] anabaseine, a natural alkaloid derivative.

⁹⁹⁷ Shprintzen or catch 22 syndrome. Incidence = c. 1/5,000 births. The term catch 22 stands for **c**ardiac defects, **a**bnormal facies, **t**hymic hypoplasia, **c**left palate, **h**ypoglycaemia, and the involvement of chromosome **22**. A more severe form of VCFS, Di George syndrome, includes absent thymus and hypocalcaemia. In fact, many clinical syndromes have been described with this deletion.(Kobrynski & Sullivan, 2007)

⁹⁹⁸ 10-20% in adulthood – the phenotype can closely resemble schizophrenia.(Bassett ea, 2003) Adolescents with 22q11.2 deletion syndrome have poor ‘source monitoring’, i.e. impaired ability to identify the origin of mental events.(Debbané ea, 2008) In common with epilepsy and a number of congenital cerebral disorders, onset of psychosis is delayed until adolescence or early adult life.(Weinberger & Marengo, 2003, p. 340)

⁹⁹⁹ ADHD, depression, anxiety, transient psychotic episodes, inappropriate emotionality, disrupted social behaviour, as well as poor functional adjustment associated with schizotypal symptoms.

Such patients may be at increased risk for seizures when given antipsychotic drugs.(Sporn ea, 2004)
 Reduced white matter volume on MRI was reported by van Amelsvoort ea.(2004)



VCFS

MRI in VCFS (abbreviated)¹⁰⁰⁰

One case of cavum septum pellucidum and hypoplastic vermis

Children with VCFS - 11% reduction in total brain volume, 16.3% and 7.5% reduction in white and grey matter volumes respectively, a relatively large frontal lobe, and a loss of normal parietal lobe asymmetry due to a reduction in grey matter on the left side

Childhood cases - relatively small lobe, superior temporal gyrus and hippocampus, the brain being small overall

Adult cases - increased prevalence of white matter hyperintensities, cavum septum pellucidum, widespread differences compared to controls in white matter bilaterally, and regional specific differences in grey matter in the left cerebellum, insula, and frontal and temporal lobes

Study reported reduced white matter anisotropy in frontal, parietal, and temporal regions as well as in tracts connecting the frontal and temporal lobes

Facial emotional processing task – reduced activation in right insula and frontal brain regions and increased activation in occipital regions

Prepulse inhibition (PPI)¹⁰⁰¹ is lower in 22q.11 deletion cases than in a sibling control group.(Sobin ea, 2005) Blackwood and Muir (2004, p. 163) point out that the gene coding for COMT is located within the small region on chromosome 22 that is deleted in VCFS. COMT genotype seems to affect brain development in VCFS.(van Amelsvoort ea, 2008) The TBX 1 gene is important in cardiac development, is involved in the deletion, and seems to be important in the development of the VCFS phenotype.

*Metachromatic leucodystrophy*¹⁰⁰² may be misdiagnosed as schizophrenia for a long time before neurological stigmata emerge.(Weinberger & Marengo, 2003, p. 340)

Paternal half-sibling studies: If paternal half-siblings (same father but different mothers) are separated early in life we can claim to have individuals who share neither intrauterine nor early maternal influences. Kety¹⁰⁰³ ea (1976) found that 13% of paternal half-siblings of schizophrenics were diagnosed as having this disorder compared with 1.6% (1 case) of 64 half-siblings of controls. These findings favour genetic transmission over other explanations.

Anticipation: This refers to increasing severity and earlier age of onset of a condition over successive generations. It has been suggested that a minority of cases of schizophrenia may have this characteristic. Di Maggio ea (2001) have reported a reduction in time of onset of psychotic symptoms and age at first hospitalisation in successive birth cohorts. Whilst reminiscent of the degeneration theories of the nineteenth century, it was hypothesised to be associated with unstable coding trinucleotide (triplet) repeat expansions.

¹⁰⁰⁰ It should be noted that reported findings are the result of comparisons with whatever controls are being employed for a particular study.

¹⁰⁰¹ Sensorimotor gating: PPI linked to haplo insufficiency of TBX1 gene (one of the genes affected in 22q11 deletion syndrome). Neonatal rats whose hippocampi are lesioned show impaired prepulse inhibition at puberty, suggesting that such an early lesion create a vulnerability to hormonal influences on neural circuits that accompany puberty.(Lipska ea, 1995)

¹⁰⁰² Aryl sulphatase deficiency.

¹⁰⁰³ Seymour Kety (1915-2000).

Work has been done on polyglutamine-expanded tracts, encoded by CAG repeats, in protein from lymphoblasts. This work has also suggested a role for a polyglutamine expansion in childhood-onset schizophrenia. These findings are reminiscent of those in Huntington's disease research. However, dynamic mutations resulting in variation trinucleotide repeats lacks convincing evidential support.(Fortune ea, 2003) *Parental age:* There is some evidence that an older father¹⁰⁰⁴ at the time of conception may be associated with increased risk for developing schizophrenia in the offspring.(Malaspina ea, 2001; Brown ea, 2002; Zammit ea, 2003a; Sipos ea, 2004) The literature does not offer a clear answer as to which offspring sex is more likely to be more affected. A Danish study found schizophrenia to be associated with having an older father; the authors speculated about new mutations, possibly X-linked.(Byrne ea, 2003) This finding receives support from Sipos ea (2004) who found that advancing paternal age¹⁰⁰⁵ increases the risk for schizophrenia in people with a negative family history. The same authors found paternal age is only weakly associated with non-schizophrenic non-affective psychosis. Fuller Torrey ea (2009) concluded that the effect of paternal age in increasing risk for schizophrenia in offspring is of 'intermediate magnitude' and applies when the father is at least aged 55 years. Rosenfield ea (2009) defined an older father as someone over 35 years of age and found that both sexes with 'paternal age-related schizophrenia' (PARS) shared the same age of onset and a similar preponderance of negative symptoms; non-PARS cases had the typical earlier age of onset and more severe negative symptoms in males; PARS cases had more severe symptoms than non-PARS cases when medication was stopped but the symptoms globally improved with antipsychotic treatment so that differences between the two groups were reduced; and the authors wondered if the aetiological pathology of PARS and non-PARS were distinct.

Other putative associations: According to Naguib (1991), paranoid schizophrenia has shown a 'consistent' association with HLA-A9. Naguib also reported 'early evidence' of an association of 'paraphrenia' with HLA-B37. The frequency of DRB1*04 alleles¹⁰⁰⁶ may be reduced in schizophrenia. In Japan, 16% of schizophrenics have DR1 (DRB1*0101) versus 10.5% of controls.(Sasaki ea, 1999) Radiation has been suggested as a possible cause of genetic mutation leading to schizophrenia.

*Obstetric complications*¹⁰⁰⁷ (OCs): A number of researchers, including O'Callaghan ea (1990), found that OCs were more common in the personal history of schizophrenic patients who had relatively early onset of illness¹⁰⁰⁸ and who lacked a family history of schizophrenia. OCs may be more important for males than females and for childhood-onset cases. An excess of pre-eclampsia and detention in care as a neonate have been reported in the histories of persons later developing schizophrenia.(Kendell ea, 1996; Jones & Cannon, 1998) The British Perinatal Mortality Survey data failed to support a connection between factors predicting perinatal mortality and the aetiology of schizophrenia.(Done ea, 1991) Others, such as McCreadie ea (1992) and Kendell ea (2000), also failed to find a connection between schizophrenia and OCs. Also, the question remains as to whether the foetus is genetically and/or environmentally predisposed to develop OCs, i.e. the direction of causation is unclear. Geddes and Lawrie (1995) speculated that selection and publication bias may inflate any connection between schizophrenia and OCs. Webb ea (2005), in a meta-analytic review, found an almost twofold higher risk of foetal death/stillbirth among offspring of women with psychoses. Harrison ea (2003), whilst finding an increased risk for non-affective psychoses for persons born in urbanised areas, were unable to incriminate OCs or parental educational status. Cannon ea,(2002) in a meta-analysis, whilst concluding that there was a small but important association between OCs and schizophrenia, pointed to the lack of statistical power to measure small and interactive effects and to a lack of detailed information about the prenatal period. Verdoux ea (1997) found an association between early onset of schizophrenia and OCs, but no connection between the latter and a family history of schizophrenia. Bersani ea (2009) found that OCs severity was significantly associated with magnetic resonance measures of ventricular enlargement, and greater OCs severity showed increased association with increasing ventricular size; these associations were independent of age at onset of schizophrenia, illness duration, and antipsychotic treatment; and OCs severity was significantly positively

¹⁰⁰⁴ And possibly an older mother.(Ekéus ea, 2006)

¹⁰⁰⁵ Advanced paternal age may also increase the risk for autism spectrum and bipolar affective disorder.

¹⁰⁰⁶ Encoding for class II HLA DR4, which is associated with rheumatoid arthritis which seems to be uncommon in schizophrenia, although the author has diagnosed just such a case.

¹⁰⁰⁷ There is room only to mention a sample of published research papers here. A major problem in this area is that a number of different OCs may turn up as relevant simply because they are interrelated.(Lewis & Zammit, 2004, p. 69) McKenna (2007, p. 185) states that this research would not stand up to the 'mildest statistical query'.

¹⁰⁰⁸ ? Foetal hypoxia → neurotoxicity → premature cortical synaptic pruning → early-onset schizophrenia.

associated with hallucinations. There is evidence that OCs may interact with genetic liability¹⁰⁰⁹ to 'produce' schizophrenia. (Kinney ea, 1998; Cannon ea, 2002) Stefanis ea (1999) found that people who experienced obstetric problems were especially likely to have a small hippocampus and we know that lesioning of neonatal rat ventral hippocampus reduces spine density in prefrontal cortex and accumbens nuclei and such animals, on reaching maturity, have excessive reactions to amphetamine. In a prospective birth cohort study, Waddington ea (2008) found a doubling of risk for schizophrenia spectrum disorder with craniofacialmidline anomalies and related functional-neural impairments which might be explained by a common relationship with brain dysmorphogenesis resulting from genetic and environmental predisposition to schizophrenia.

Low birth weight (< 2,500 grams) has been reported in people who later develop schizophrenia¹⁰¹⁰. In males this may be associated with poorer premorbid social and cognitive abilities, and with impairment of adult cognitive function. In fact, low birth weight may be one factor in determining which MZ twin develops schizophrenia. (Stabenau & Pollin, 1993) Jablensky ea (2005) found increased risk for pregnancy, birth and neonatal complications¹⁰¹¹ among both schizophrenic and affective disorder¹⁰¹² patients. Schizophrenia in the mother was associated with heightened risk for placental abruption, small/light babies, and offspring with congenital cardiovascular anomalies. Neonatal complications were more common in winter, whereas low birth weight peaked in spring. OCs¹⁰¹³ more often succeeded diagnosis of psychiatric illness than preceded it. Rifkin ea (1994) suggested that neurodevelopmental impairment caused both poor foetal growth and later schizophrenia. Alvir ea (1999), in a small number study, found poor response to treatment in first episode schizophrenia to be associated with a history of OCs and larger lateral ventricles. When Kirov ea (1996) removed cases with a history of OCs (mainly males) from their series of 73 schizophrenics, they found that the sex difference in the age of onset disappeared! Interestingly, for reasons that are not fully understood, birth and delivery complications *in general* may be more common in boys. (Eogan ea, 2003)

There has been suggestions that schizophrenia may be associated with rhesus incompatibility. (Hollister ea, 1996)

First trimester maternal starvation retrospectively correlated with schizophrenia in offspring. (e.g. Susser & Lin, 1992) Poor nutrition might affect brain development¹⁰¹⁴, as might toxins¹⁰¹⁵ or diuretic drugs used to treat hypertension during the third trimester. (Sørensen ea, 2003) Sørensen ea (2004) reported an association between second trimester analgesic-taking and risk for schizophrenia in offspring.¹⁰¹⁶ Susser and Lin (1992) found an increased risk for schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945. Similar findings were reported for the Chinese famine of 1959-1961. (St. Claire ea, 2005) However, there is also a reported increased risk for schizophrenia for people born in the Netherlands during 1940¹⁰¹⁷, relative to persons born during 1938-9 or 1941-43. (Van Os & Selton, 1998) Also, Neugebauer ea (1999) found an association between antisocial personality disorder in the offspring of mothers exposed to the same Dutch Hunger Winter.

Findings of an excess of schizophrenia from unwanted pregnancies (Myhrman ea, 1996) do not tell us why the pregnancies were unwanted. Other reported associations with later schizophrenia include maternal stress during pregnancy, vacuum extraction, prolonged labour, preterm delivery¹⁰¹⁸, low birth weight¹⁰¹⁹, smallness for dates, and foetal malformations. Hypoxia-ischaemia may be a common perinatal risk factor in the histories of both schizophrenic (Dalman ea, 2001) and other non-affective psychosis and this may apply

¹⁰⁰⁹ Indicated by eye tracking dysfunction or comparative gray matter and CSF abnormalities in schizophrenic patients, their siblings and normals.

¹⁰¹⁰ As has short gestation and depression in the mother during pregnancy.

¹⁰¹¹ Including placental abnormalities, antepartum haemorrhage, and foetal distress.

¹⁰¹² Scott ea (2006) reviewed the literature and found no reliable evidence for a connection between exposure to OCs and bipolar disorder.

¹⁰¹³ Other than low weight babies and congenital anomalies.

¹⁰¹⁴ Indeed MRI has shown reduced brain size and various abnormalities, such as white matter hyperintensities.

¹⁰¹⁵ Alcohol, amphetamine, retinoids, etc.

¹⁰¹⁶ Some of the drugs taken by mothers in the study are now generally obsolete, the study lacked statistical power in relation to the effects of individual chemicals, and information on dosage was unavailable.

¹⁰¹⁷ German invasion.

¹⁰¹⁸ Maternal distress in later pregnancy, as shown on the GHQ, has been shown to be a risk factor for preterm delivery in Danish non-psychiatric populations.

¹⁰¹⁹ A modest risk factor for schizophrenia.

to both sexes. Large population-based samples are needed to clarify the relationship between OCs and schizophrenia.(Thomas ea, 2001) Caution is required in interpreting results (Jablensky, 2003, p. 218) and reliance on maternal recall alone is susceptible to bias.(McIntosh ea, 2002)

Cannon ea (2002) classify three groups of **complications** that may have significant associations with schizophrenia. These were derived from a meta-analysis of prospective studies and are:

- complications of pregnancy (bleeding, diabetes, rhesus incompatibility, preeclampsia),
- abnormal foetal growth and development (low birth weight, congenital malformations, reduced head circumference), and
- delivery complications (uterine atony, asphyxia, emergency Caesarean section).

Breastfeeding: There is no convincing evidence¹⁰²⁰ of an association between been breastfed or not and developing schizophrenia.(Mukherjee & Galanis, 2001)

Dermatoglyphics: A number of authors (e.g. Mellor, 1992) have reported differences in the skin ridge pattern¹⁰²¹ between schizophrenic patients and controls, the latter including co-twins in MZ pairs. The relatives of schizophrenics may also have such abnormalities.(Avila ea, 2003)

Neuropathology and neurophysiology: The second trimester is a critical period for massive neuronal migration to the cortex¹⁰²² and there is evidence to suggest that this does not occur normally in at least some cases of schizophrenia, e.g. the finding of heterotopic clusters of neurones in the entorhinal cortex, or selective displacement of interstitial frontal white matter neurones.(e.g. Akbarian ea, 1996) However, attempts to replicate cell disarray have been problematic.(McKenna, 2007, p. 134) Gogtay ea (2008) used tensor-based morphometry to study 12 cases of childhood-onset schizophrenia and 12 healthy controls over a 5-year period and found that childhood-onset schizophrenia was associated with up to 2.2% slower annual growth rates in white matter, especially in the right hemisphere.

Popken ea (2000) reviewed the literature and reported certain consistent findings: smaller cortical neurones, diminished arborisation of axons and dendrites, and a diminished number of thalamic neurones (especially in mediodorsal nucleus and especially the subnucleus projecting to dorsolateral prefrontal cortex).

Polysialic acid-rich neural adhesion molecule is involved in regeneration and plasticity of neurones and may be reduced in schizophrenic patients' hippocampi; mice who are depleted in polysialic acid-rich neural adhesion molecule isoform 180 (PSA-NCAM-180) show neuronal migration and cytoarchitectural problems.(Lipska & Weinberger, 2003, p. 395) Synaptic density peaks in childhood in the human frontal cortex, decreasing by 30-40% during adolescence because of progressive elimination of synaptic connections. Excess pruning has been suggested as a cause of hallucinations, as has abnormal co-activation of white matter tracts leading to confusion as to the source of inner speech¹⁰²³.(Hubl ea, 2004; Shergill ea, 2004) Schizophrenia might be a cortical or a subcortical disorder, the latter involving such structures as the basal ganglia or thalamus where integration and co-ordination of neural function is undertaken.

Bogerts ea (1985) reported that the brains of schizophrenic patients who died before modern treatments¹⁰²⁴ became available had reduced size of the amygdala, hippocampus, and parahippocampal gyrus and globus pallidus. McDonald (2004, p. 189) states that the morphology of schizophrenia and bipolar disorder are distinct but overlapping: the former is associated with subcortical and frontotemporal volumetric deficits, but grey matter volume is normal in psychotic bipolar disorder; and both conditions are characterised by volumetric deficits in white matter, with temporoparietal overlap. Other research findings are listed in the box.

¹⁰²⁰ And methodological problems, e.g. lack of statistical significance, small sample size, poor information on the general population.

¹⁰²¹ Since dermal ridges appear in the third to fifth months of gestation, the inference is that the cause of these abnormal dermatoglyphics preceded those dates.

¹⁰²² And migration of dermal cells to form skin ridges.

¹⁰²³ However, Langdon ea (2009) found no significant difference between healthy controls and schizophrenic subjects with auditory verbal hallucinations in terms of inner speech and the phenomenology of the hallucinations (e.g. third-person) did not relate to inner speech. Nevertheless, Simons ea (2009), using fMRI with 15 patients with schizophrenia and 12 healthy controls who listened to sentences and imagined sentences, found attenuated deactivation of the left superior temporal gyrus in schizophrenic patients whilst they processed inner speech, suggesting a problem with self-monitoring (i.e. my thoughts or extraneous words?).

¹⁰²⁴ Including ECT and insulin treatment.

Neuropathological findings in schizophrenia¹⁰²⁵

Reduction in all cell types in the mediodorsal thalamic and accumbens nuclei
 Smaller (than in controls) neurones in hippocampal areas (e.g. entorhinal cortex) thought to maintain two-way connections with the cerebral cortex
 Reduced numbers of small neurones in the superficial lamina and increased numbers of larger numbers in deeper layers of the prefrontal and cingulate cortices

Increased neuronal density in the cerebral cortex and in areas of right hippocampus
 Cytoarchitectural asymmetry between hippocampi
 Increased CSF and reduced frontal lobe tissue
 Affected MZ twin had larger cerebral ventricles and smaller hippocampi bilaterally than unaffected twin
 Reduced density of the largest cortico-cortical projection neurones of sublayer IIIc of the prefrontal cortex
 Cognitive deterioration in older schizophrenics did not correlate with age-related degeneration
 Most cases of cognitive impairment not due to Alzheimer's disease, but mild Alzheimer-like pathology might reduce cognitive reserve in chronic schizophrenia (scz)
 Significantly smaller L superior temporal gyrus in both sexes in scz; total volumes of temporal lobe grey and white matter also significantly smaller, especially on L
 Altered dopaminergic innervation of prefrontal cortex area 9 (did not seem to be due to medication)
 Levels of the synaptic vesicle protein synaptophysin and the presynaptic protein SNAP-25, but not their mRNAs (other studies have found reduction in this mRNA in some brain regions), are reduced in scz, suggesting 'hypofrontality' might be due to abnormal structure or function in prefrontal cortex
 Levels of L1 and Thy-1 cell adhesion molecules (CAMs) normal in prefrontal cortex
 Increased fibre density in fornix of male scz
 Increased mononuclear phagocytes/macrophages in CSF during acute psychotic episode, cytology normalising during conventional neuroleptic therapy

Dendritic spine density reduced in layer 3 of dorsolateral prefrontal cortex (DLPFC) in scz
 Mean gyrification index (a ratio involving line of gyral surface and inner line of skull) on R side increased in M scz only
 Scz of both sexes had reduced volumes of L parahippocampal and fusiform gyri; normal L>R volume asymmetry reversed for both structures in scz; and degree of anomaly of asymmetry for both gyri increased with age of onset in M but not F scz
 Reduced spine density of subicular apical dendrites in scz and mood disorders (in latter case it is related to strong family history of major psychiatric disorders)
 Reduced levels of glycogen-synthase kinase-3 (protein kinase involved in signal transduction and in neurodevelopment) in frontal cortex in scz (*antipsychotic drugs may treat psychotic symptoms, at least partly, by modulating levels and activity of Akt/glycogen-synthase kinase-3 [GSK-3] and wingless (Wnt)-related intracellular signalling*: Freyberg et al, 2010)
 Having found changes in mitogen¹⁰²⁶ activated protein (MAP) kinase in scz after death, then found increase in protein levels of ELK-1, CREB and ATF-2 in cerebellar vermis; given critical role of MAP kinase pathway in memory consolidation and long term neuronal plasticity, and the role of the cerebellum in memory, the results are no surprise (small Purkinje cell size in vermis in scz has also been reported)
 Transcriptional and post-transcriptional glutamate receptor expression reduced in thalamus in scz
 No volumetric abnormalities of frontal in scz (TJ Crow's group)
 MRI and postmortem evidence of R hypergyria in family with multiple cases of scz
 Decreased somal size of prefrontal cortex in scz and smaller deep layer 3 pyramidal neurones
 Fewer projections from mediodorsal thalamic nucleus to prefrontal cortex
 Abnormal densities and ratios of olfactory epithelium in scz
 Scz have smaller and less than normal numbers of neurones in some thalamic nuclei
 Consistent volume reduction of amygdala not consistent finding in scz
 No evidence of a primary alteration of the hippocampus in schizophrenia
 Increased phosphate-activated glutaminase and glutamic acid decarboxylase activities in DLPFC in scz suggests dysregulated glutamatergic/GABAergic state
 Examination of single neurones in entorhinal cortex in scz for gene expression found marked differences from controls in various G-protein-coupled receptor-signalling transcripts, glutamate receptor subunits, synaptic proteins, etc
 DARPP-32 reduced in DLPFC in scz (DARPP-32 is localised to neurones with DA receptors. It is a strong inhibitor of protein phosphate 1, which plays an important role in dopaminergic and glutamatergic signalling and in integrating these two pathways.)
 Compared to normals, scz at postmortem only had significant smaller (12% difference) frontal gray matter volume
 Monoclonal antibody against microtubule-associated protein MAP2 (a dendritic protein) to label interstitial white matter neurones in anterior parahippocampal gyrus: suggests abnormality in residua of cortical subplate (? migration problem or problem with pattern of programmed cell death)
 No differences in cerebellum between DSM-III male scz and male controls
 Amyloid β -peptide levels in scz without Alzheimer's disease do not differ from normals (measured using antibodies)
 Reduced NR1 subunit (of NMDA receptor) transcript expression restricted to exon 2-containing isoforms; increased expression of NMDA receptor-associated postsynaptic density proteins NF-L, PSD95, and SAP102 detected in thalamus in scz

¹⁰²⁵ Roughly in order of publication. It should be noted that Elmer Ernest Southard (1876-1920) of Boston reported ventriculomegaly in deceased schizophrenic patients (no controls used) in the *American Journal of Insanity* in 1915 (January, p. 639).

¹⁰²⁶ A *mitogen* is an agent that induces mitosis and cell proliferation.

Decreased thalamic expression of homeobox gene DLX1 (required for production, migration, and differentiation of neocortical, hippocampal, and olfactory bulb GABA-ergic interneurons in mice; DLX1 and DLX2 in humans are closely linked at chromosome 2q32) in patients with scz and in bipolar patients with a history of psychosis

Relatively small sample failed to find any change in hippocampal pyramidal neuronal cell size in scz

Glial cell loss in anterior cingulate cortex in scz

Density of GABA interneurons expressing NMDA NR2A subunit is decreased in ant cingulate cortex in scz and bipolar disorder (note: GABA interneuronal activity is modulated by glutamatergic input from pyramidal cells)

Normal Heschl's gyrus found in scz

Scz patients had lower levels of spinophilin (neurabin II, a dendritic spine marker) mRNA in CA4 (hilus), CA3, subiculum, and entorhinal cortex than did normal hippocampal formations; mood disorder group had similar findings to scz; MAP2 and cyclophilin mRNA (housekeeping gene control) did not differ between scz, mood disorder, and normals: evidence for abnormal dendritic spines in scz and mood disorders (spines are target of most glutamatergic synapses)

Increased neuronal density and reduced interneuronal **neuropil**¹⁰²⁷ in primary visual area in scz

Abnormal DNA methylation of genes related to neurodevelopment and synaptic plasticity in occipital cortex in scz

High levels of H3-(methyl)arginine 17 associated with downregulated metabolic gene expression in prefrontal cortex (PFC) of some cases of scz: histone modifications may contribute to PFC dysfunction (4 core histones together with base pairs of genomic DNA wrapped around them compose the basic units of chromatin [nucleosomes]; chromatin fibres consist of arrays of nucleosomes connected by histones and DNA)

Thalamic dopaminergic abnormalities in scz are at level of intracellular integration of DA signalling with other neurotransmitter systems, probably including glutamate

Greater exposure to typical antipsychotics leads to thicker ant cingulate gyrus

Small study of DLPFC at postmortem in scz showed no increase in neuronal density but there was loss or reversal of asymmetry in cortical layer 3

2-dimensional electrophoresis of DLPFC in scz, bipolar affective disorder (BAD) and mentally normal controls to look for abnormal proteins: scz and BAD had differences from controls; mass spectrometry identified 15 scz-associated and 51 BAD-associated proteins; most affected were synaptic proteins in scz and metabolic and mitochondrial proteins in BAD; majority of abnormally expressed synaptic-associated proteins in BAD were isoforms of the septin family; findings are evidence for synaptic pathology in scz and metabolic dysfunction in BAD

MRI evidence of prefrontal volume deficits in scz that mainly affect areas (orbitofrontal) needed to think socially

GABA transmission appears to be decreased in cortex of cerebellum in scz

Antibody testing of post-mortem brain in scz found increased glutamate carboxypeptidase (GCP II) expression and low mGluR3 (a group II metabotropic glutamate receptor) expression in DLPFC suggesting that N-acetyl-aspartyl-glutamate (NAAG, a specific endogenous mGluR3 agonist) –mediated signalling is impaired; also, mGluR3 receptor appears to be involved in antipsychotic action of mGluR2/mGluR3 agonists

Postmortem study of anterior cingulate brain sections (BAD, major depressive disorder [MDD], schizophrenia, and controls) determined oxidative stress by analysing 4-hydroxynonenal (4-HNE), a major product of lipid metabolism; 4-HNE levels raised by 59%, 47% and not at all in BAD, schizophrenia, and MDD respectively; oxidative damage may contribute to BAD and schizophrenia

In a post-mortem study case-control study, schizophrenic subjects had large increases in chondroitin sulphate proteoglycans (CSPGs¹⁰²⁸)-positive glial cells in amygdala and entorhinal cortex (CSPG changes were negligible in bipolar disorder)

Reveley ea (1982) suggested that cerebral ventricular size might be under genetic control: where only one of a pair of twins has schizophrenia it is the one with the larger ventricles who has the illness. These findings find support from other workers.(e.g. Suddath ea, 1990). BDNF Met allele carriers have significantly greater decreases in frontal grey matter volume with reciprocal increases in the lateral ventricles and sulcal CSF than Val homozygous patients.(Ho ea, 2007)

Lateral ventriculomegaly in schizophrenia seems to be more marked in males.(e.g. Flaum ea, 1990)

Crow (1990) suggested that enlargement of the temporal horn of the lateral ventricle in schizophrenia is selective to the left side of the brain.

Knable ea (1998) point to the non-progression of abnormal findings in schizophrenia¹⁰²⁹ and the absence of gliosis as evidence for a neurodevelopmental¹⁰³⁰ (versus neurodegenerative¹⁰³¹) process. However, Pantelis ea,(2003) in an MRI study, examined people with 'prodromal signs of psychosis' and re-examined them after 12 months: at baseline, those who would develop psychosis had less grey matter in right medial temporal, lateral temporal and inferior frontal cortices and in cingulate cortex bilaterally, while after developing psychosis grey matter was reduced in left parahippocampal, fusiform (occipitotemporal), orbitofrontal and cerebellar cortices and cingulate gyri; in those not becoming psychotic changes over the

¹⁰²⁷ Neuropil: blood vessels, glia, axons, and dendrites.

¹⁰²⁸ CSPGs are an important part of brain extracellular matrix that is involved in regulating developmental and adult neural functioning.

¹⁰²⁹ Big cerebral ventricles, small medial temporal lobe structures, aberrant function of prefrontal cortex.

¹⁰³⁰ Ziermans ea (2009) performed MRI on young adolescents at ultra high risk for psychosis and were unable to demonstrate any gross neuroanatomical changes! They wondered if changes were present but too subtle to see or if they develop later.

¹⁰³¹ See McWilliams and O'Callaghan.(2007)

year were restricted to the cerebellum; therefore, it was concluded, some grey matter changes precede and others develop in association with first expression of psychosis¹⁰³². In another MRI study, with a mean of 3 years between scans, Ho ea (2003) found progressive reduction in frontal lobe white matter (and increases in cerebrospinal fluid volume) during the early stages of schizophrenia. Cahn ea (2006) found that progressive brain volume changes on MRI, especially of grey matter, were associated with clinical and functional outcome five years after a first-episode of schizophrenia. Also, Brans ea (2008a) repeated MRI after a 5-year interval and found excessive whole brain and cerebral grey matter volume decrease in schizophrenia patients¹⁰³³ compared to their same-sex siblings and healthy matched controls. The same group (Brans ea, 2008b) used MRI in a 5-year follow-up of MZ and DZ twins discordant for schizophrenia and healthy comparison twin pairs: patients with schizophrenia and their unaffected co-twins showed significant decreases over time in whole brain and temporal and frontal lobe volumes and such changes could at least partly be explained by illness-related genetic factors.

Treatment-resistant schizophrenia has been described in association with cerebral hemiatrophy¹⁰³⁴. Other associations with schizophrenia include an excess of midline brain malformations, e.g. cavum septum pellucidum (found at all stages of schizophrenia and, less commonly, in affective disorders and schizotypal disorder¹⁰³⁵, and, less commonly again, in about 13% of normals), agenesis of corpus callosum, and aqueductal stenosis.

According to Nasrallah and Smeltzer, (2002, p. 134) against the idea that schizophrenia represents a ‘static encephalopathy’ are unpredictability of clinical course, great differences in outcome, a tendency for positive (productive) symptoms to be replaced by negative symptoms¹⁰³⁶ over time, characteristics of the cognitive deficit, and a tendency to ‘burnout’¹⁰³⁷ after years of progression. They suggest that there may be a neurodegenerative process superimposed on faulty neurodevelopment. They also suggest that atypical antipsychotic drugs may have a neuroprotective effect that inhibits degeneration. Murray (2008) states that increased striatal D2 receptors in mice may cause schizophrenia-like deficits in behaviour and cognition that could represent a model for negative symptoms. Keefe ea (1999) reviewed fifteen efficacy studies and found that, despite methodological problems, there was support for improvement in verbal fluency¹⁰³⁸, digit-symbol substitution, fine motor function and executive functions in patients treated with atypicals. However, despite such gains, the performance of schizophrenic patients failed to reach normal levels. Krabbendam and Jolles (2002) have reviewed the claim that conventional antipsychotic drugs have a negative effect on cognition and found any such action to be minor (Similarly, atypical drugs have a modest positive effect on neurocognition¹⁰³⁹, with little difference between individual drugs: Keefe ea, 2007; Cuesta ea, 2009). Nevertheless, they correctly point out that the anticholinergic actions of drugs may be a real problem¹⁰⁴⁰. Importantly, Davidson ea (2009) examined the effects of haloperidol versus four atypical drugs¹⁰⁴¹ on cognition in schizophreniform patients and first-episode schizophrenia patients and found that all the drugs moderately and equally improved performance and that such improvement was weakly related to changes in the PANS scores.

There may be reduced *cerebral laterality* in schizophrenia. Evidence for this comes from linguistic analysis¹⁰⁴², chimeric stimuli¹⁰⁴³, EEG studies¹⁰⁴⁴, dichotic listening tests¹⁰⁴⁵, dopamine studies, and

¹⁰³² This is, of course, not a very long follow up period and a ‘prodrome’ is not always easily distinguishable from early symptoms

¹⁰³³ Mean duration of illness = 19.6 years (s.d. = 11.5).

¹⁰³⁴ Dyke-Davidoff syndrome.

¹⁰³⁵ From Rado’s 1950 ‘schizotype’, short for ‘schizophrenic phenotype’. McKenna (2007, p. 435) states that Spitzer adopted Kety’s ‘borderline schizophrenia’ and renamed it schizotypal personality for DSM-III.

¹⁰³⁶ Which may represent the core symptoms of the disorder. (Ho ea, 2003, p. 382)

¹⁰³⁷ Reaching a plateau without further deterioration.

¹⁰³⁸ A meta-analysis (Henry & Crawford, 2005) suggested that verbal fluency problems in schizophrenia are but part of a generalised intellectual dysfunction.

¹⁰³⁹ Because studies of the effects of antipsychotic drugs differed due to the use of different memory tests the NIMH introduced the MATRICS Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative aimed at developing a common test battery. (see Harvey & Cornblatt [2008] for an introduction)

¹⁰⁴⁰ Drimer ea (2004) withdrew chronic anticholinergic drugs from older schizophrenic patients: extrapyramidal symptoms did not worsen and cognition improved. See also Vinogradov ea (2009b) who found that anticholinergic load interferes with cognitive training in schizophrenia.

¹⁰⁴¹ Amisulpride, olanzapine, quetiapine, and ziprasidone.

¹⁰⁴² Schizophrenics have less syntactically complex speech that contains more errors than either manics or controls – healthy controls, unlike schizophrenic patients, activate the posterior part of the right middle temporal and left superior frontal gyri when forming complex sentences. (Kircher ea, 2005)

neuroimaging¹⁰⁴⁶. Different authors suggest that the ‘problem’ may be in the right or the left cerebral hemisphere, and some studies found no evidence for a laterality problem at all. Crow (1995; see also above re protocadherin XY) hypothesised that psychoses are a product of human evolution, because of variation in genes controlling hemispheric asymmetry; he had earlier stated that psychosis may be related to increased complexity of neocortical structures associated with the evolution of language; and he would later describe the nuclear symptoms of schizophrenia as ‘language at the end of its tether’. Because of callosal constraints, language evolved by a process of hemispheric specialisation. ‘Phonological output sequence’ became localised to the dominant (for language) hemisphere, whereas its associations or ‘signfields’ were lateralised in part to the other half of the brain. Concepts (thoughts) are translated via a bi-hemispheric interaction into phonemes (speech) by the speaker in frontal association areas, and decoded back into concepts (meanings) by the hearer in occipito-temporal-parietal areas. According to Tim Crow, the psychotic person cannot distinguish the phonemic signals generated by the hearer from his own thoughts, or from signals that he receives from an interlocutor. Put more simply, his brain interprets his own thoughts as foreign. The question arises about the heritability of first rank symptoms, put at zero by some; but Loftus ea,(2000) who extracted nuclear/Schneiderian symptoms from case notes of and interviews with sibling pairs with DSM-III-R schizophrenia or schizoaffective disorder, found that some such symptoms ‘show a degree of familiarity and therefore perhaps heritability’. According to Ceccherini-Nelli and Crow,(2003) the *Clinical Language Disorder Rating Scale (CLANG)*¹⁰⁴⁷ is a reliable and valid instrument for assessing language disturbance in psychosis, and language disturbance is more specific than first-rank symptoms in the diagnosis of ICD-10 schizophrenia. However, the controls used were non-psychotic depressives, so no attempt was made to distinguish schizophrenia from mania; it was a non-blinded study; and instruments other than the CLANG were not employed.

Liddle (2001, p. 94) finds that human minds have become relatively independent of outside influence, allowing for a more flexible response to an ever-changing external world by utilising stored memories to construct theories about the future. He believes that reality distortion ultimately emanates from a confusion of ‘mental representations triggered by current external circumstances’ with ‘representations of past situations and representations of hypothetical situations’.

The *developmentally reduced synaptic connectivity (DRSC)* theory suggests that schizophrenia results from reduced synaptic connectivity due to perinatal and adolescent disturbances that lead to too few dendrites and synapses. Tissue loss, according to this theory, represents a loss of neurophil¹⁰⁴⁸ rather than neurones. Electrophysiological studies using a number of perceptual tasks have shown changes in auditory event-related potentials that distinguish schizophrenic patients from controls. The P3 component is a positive deflection recorded from the vertex about 300 milliseconds after a stimulus. Blackwood ea (1987), from their controlled studies, suggest that a prolonged P3 latency and reduced P3 amplitude indicate an impairment of auditory processing in some patients with schizophrenia which is independent of the presence of acute psychotic symptoms and is not influenced by neuroleptic treatment. There is some evidence that auditory P3 amplitude may decrease with illness duration.(van der Stelt ea, 2004) It should be noted that, despite the fact that the P3 component of the visual evoked response is often spared in these patients, there is a disturbance of visual attention also in schizophrenia as evidenced by reduced frontal P2a and posterior N2b event related components.(Potts ea, 2002) Work with event-related potentials suggest a neurophysiological impairment in the maintenance of selective attention and the cognitive processes associated with target detection in schizophrenia, probably due to dysfunction of frontostriatal pathways.(O’Shea, 1997; Mathalon ea, 2004 – work using visual target and competing visual stimuli were

¹⁰⁴³ Faces are presented with one side showing one emotion and the other side showing a different emotion.(e.g. Gooding & Tallent, 2002)

¹⁰⁴⁴ E.g. failure to show the normal left-sided superiority for phonetic processing as measured by event-related potentials; EEG and MEG combined point to left hemisphere dysfunction as being strongly related to auditory sensory gating deficit in schizophrenia.(Thoma ea, 2003)

¹⁰⁴⁵ If confined to testing for consonant-vowel or fused word tasks.

¹⁰⁴⁶ E.g. fMRI differences: controls activate both sensorimotor cortices during thumb opposition whereas schizophrenics show decreased activation of these areas; and MRI differences: amount of speech produced when talking about inkblots correlates with left and right superior temporal gyri respectively in controls and patients.

¹⁰⁴⁷ CLANG: 17 observer-rated items, such as unclear links and excess or lack of details, anchored on a four-point severity scale.(Chen ea, 1996)

¹⁰⁴⁸ Dendrites, axons, and synapses.

interpreted by the authors as suggesting anterior cingulate dysfunction [Yücel ea, 2002]) Other workers have reported reduced P3 amplitude¹⁰⁴⁹ in the close relatives of schizophrenics and in people with schizotypal (personality) disorder, while still others suggest that reduced amplitude of the P3 component on the left side only may characterise early schizophrenia. According to Butler ea (2005) deficits in early-stage visual processing predict higher cognitive deficits. Myles-Worsley (2002), looking at multiplex families, found impaired auditory sensory gating (independent of treatment, including doses) in schizophrenia patients (67% had abnormal P50 ratios) and their first-degree relatives (51.8%) compared to normals (10.3%) as measured by P50. According to Hall ea, (2007) event-related potential indices are potentially valid endophenotypes¹⁰⁵⁰ for schizophrenia, with P50 suppression and P300 amplitude showing the closest genetic relationship to schizophrenia. Greenwood ea (2007) looked at 183 families containing probands with schizophrenia and calculated heritability for pre-pulse inhibition of startle response, P50 event-related potential suppression, antisaccade task for eye movements, *Continuous Performance Test*, *California Verbal Learning Test* (second edition), and *Letter Number Sequencing Test*; all showed significant heritability but also significant environmental correlations. Sánchez-Moria ea (2008) found evidence supporting the presence of a P50 sensory gating deficit in both schizophrenia and euthymic bipolar disorder, implying that this deficit represents vulnerability to psychosis across diagnoses. Decreased neuregulin 1-induced activation of phosphoinositide 3' kinase (PI3K)/AKT system has been reported in association with impaired sensory gating in first-episode schizophrenia (Kéri ea, 2010), neuregulin 1 being involved in intracellular signalling. This finding may be important because antipsychotic drugs may ameliorate psychotic symptoms, at least in part, by modulating levels and activity of Akt/glycogen-synthase kinase-3 [GSK-3].

Using EEG coherence measures, Norman ea (1997) found a relationship between left fronto-temporal connectivity and reality distortion, especially in males. Slewa-Younan ea (2004) employed a conventional auditory odd-ball task in men and women with chronic or first-episode schizophrenia and matched controls; phase synchronous gamma (40 Hz) activity was extracted from the EEG: chronic cases, especially females, showed decreased global functional connectivity (lower gamma phase synchrony); while first-episode cases showed a general decrease in the speed of frontal connectivity, the speed of global connectivity was faster in female patients; the results suggest that female schizophrenics experience further breakdown in cerebral network connectivity as the disease becomes chronic. Symond ea (2005) reported that first-episode schizophrenia patients had decreased magnitude and delayed latency for global gamma 1 synchrony relative to controls, but no difference to controls in gamma 2 synchrony. Wynn ea (2005) found decreased gamma activity and failure of lateralisation of activity to the right hemisphere during masking. A decrease in EEG-evoked responses in the gamma band when transcranial magnetic stimulation was applied to directly stimulate frontal cortex suggested a possible intrinsic dysfunction in frontal thalamocortical circuits in schizophrenia.(Ferrarelli ea, 2008)

Other EEG findings include

Reduced delta sleep in unmedicated schizophrenic patients
 Greater negativity of the N400 on the EEG in both schizophrenia and schizotypy in response to reading or hearing sentences
 Reduced N400 in schizophrenic patients to unprimed words
 The P50 wave following the second of two auditory clicks is suppressed or 'gated' in normals whereas patients with schizotypal personality disorder or schizophrenia (and the latter's relatives) have much less P50 suppression than do healthy controls
 Findings suggestive of a disturbance in processing relevant and irrelevant information
 Reversed P300 temporal area asymmetry (smaller on the left) in first-episode schizophrenia that may be explained by reduced gray matter volume of left posterior superior temporal gyrus on MRI

Light ea (2000) found that conventional neuroleptics failed to normalise P50 suppression in people with schizophrenia, whereas risperidone, olanzapine and clozapine were able to do so. Adler ea (2004) found that clozapine improved P50 gating more than did olanzapine, risperidone, quetiapine or typical antipsychotic drugs. It should be noted, however, that Arnfred ea,(2003) in a controlled study of auditory evoked potentials in 12 unmedicated schizophrenic outpatients, found P50 gating to be normal.

¹⁰⁴⁹ Or temporoparietal reduction and frontal increase.(Winterer ea, 2003)

¹⁰⁵⁰ According to Martin ea (2007) P50 ratio and frequency of leading saccades identified subjects with schizophrenia and bipolar disorders with high sensitivity (95%) and specificity (83%) with some schizoaffectives being being classified with schizophrenia and others with bipolar.

The visual system has two main components: a dorsal¹⁰⁵¹ and a ventral¹⁰⁵² stream. Doninger *et al.* (2002) tested the ability of schizophrenic patients to recognise complete objects based on fragmentary information (i.e. perceptual closure, e.g. recognising a face behind an open venetian blind). Nc1 (closure negativity, an index of perceptual closure generated in the visual cortex), and the preceding positive (P1) and negative (N1) event-related potentials (ERPs) were examined. The patients were significantly impaired in this ability; there was impaired generation of the Nc1, significantly reduced amplitude of visual P1 (especially over dorsal stream sites), and intact generation of visual N1. Work in Dublin by Yeap *et al.* (2006) demonstrated a deficit in early visual processing (P1 amplitude reductions) in well first-degree relatives of people with schizophrenia. Kéri *et al.* (2005) suggest that multiple visual information processing deficits derive from dysfunction of the magnocellular pathway, leading to impaired attentional modulation of perceptual organisation and of natural image organisation.

Hong *et al.* (2008) found that gating of the theta-alpha-band responses of controls were significantly different from schizophrenia patients and their first-degree relatives. Furthermore, heritability of this band (0.49-0.83) was at least four times higher than the P50 heritability estimate. Thus, the authors suggest that this measure may be a superior one for genetic studies of the gating deficit in schizophrenia,

Excitatory lateral connections in early stage visual cortical processing may be specifically impaired in schizophrenia, but not in bipolar disorder. (Kéri *et al.*, 2005) This may contribute to complaints such as unclear seeing, partial or skewed sight, disrupted rectilinearity, and abnormal figure-ground segregation.

In chronic schizophrenia there is some evidence of increased skin conductance activity at rest, and in socially demanding conditions the skin conductance level and variability was increased in the right hand. Asymmetry of skin conductance may therefore be a characteristic of the chronic form of the illness (White *et al.*, 1987). A number of authors have produced evidence for impaired autonomic habituation in schizophrenia; in fact, it has been suggested (Zahn *et al.*, 1997) that in childhood-onset cases a combination of low elicited skin conductance activity (SDA) and high levels of spontaneous SDA may be specific for schizophrenia. Holt *et al.* (2009) reported increased neural response to innocuous stimuli and increased arousal levels in schizophrenic subjects.

Eye-tracking¹⁰⁵³ (smooth pursuit of a spot) abnormalities are not specific to schizophrenia, having been reported in depression, bipolar disorder, OCD and in delusional disorder, (Campana *et al.*, 1998; Lencer *et al.*, 2004; Gooding *et al.*, 2004) although they appear to be inherited with schizophrenia. (O'Shea, 1997) Such studies have been criticised on methodological and interpretational grounds. Over 80% of people with schizophrenia do however have abnormal smooth pursuit tracking with about one in three of their relatives having similar problems. (e.g. Kathmann *et al.*, 2003) Saccadic abnormalities¹⁰⁵⁴ are also reported in schizophrenia. (O'Shea, 1997) Both these and smooth pursuit abnormalities seem to be present from the start of the disorder. The fundamental problem may be one of poor sensory integration in general.¹⁰⁵⁵ There may be an abnormal frontostriatal network that normally suppresses automatic eye movements (Raemaekers *et al.*, 2002) and/or an abnormality of the frontal eye field. (Lencer *et al.*, 2004) Saccadic abnormalities seem to be more common in schizophrenics than in their relatives but more common in the latter than in affective states, who in turn are more affected than healthy people. (Csernansky, 2002) Saccadic task performance is more stable over time in schizophrenia than in bipolar cases, which supports a trait-like phenomenon in the former group. (Gooding *et al.*, 2004) Indeed, saccade and smooth pursuit dysfunction may be endophenotypes of schizophrenia¹⁰⁵⁶. (Kallimani *et al.*, 2009) Harris *et al.* (2006) found that deficits in the voluntary control of spatial attention persisted after treatment in antipsychotic-naïve first-episode schizophrenia but that the deficits were worse whilst the patients were acutely ill. Lencer *et al.* (2008) found that second generation (atypical) antipsychotic drugs impaired already abnormal smooth pursuit performance in antipsychotic-naïve patients with schizophrenia. There was some partial normalisation at one year. In a study conducted by Landgraf *et al.* (2008) schizophrenic patients and their siblings showed

¹⁰⁵¹ Input from magnocellular division of lateral geniculate nucleus and extends from early visual areas through the occipitoparietal cortex.

¹⁰⁵² Input from parvocellular division of lateral geniculate nucleus and extends through the occipitotemporal cortex.

¹⁰⁵³ This gives information about integrity of neural networks mediating motion perception, sensorimotor transformation, and cognitive processes such as prediction. (Lencer *et al.*, 2008)

¹⁰⁵⁴ Subject fixates central dot that steps randomly to right or left. When target steps into periphery, subject has to look to side opposite to target.

¹⁰⁵⁵ Abnormal proprioception in schizophrenia has been recognised since the 1950s. (Rado, 1953)

¹⁰⁵⁶ However, active fixation may be state-dependent. (Kallimani *et al.*, 2009)

elevated memory-guides saccade¹⁰⁵⁷ error rates relative to controls, reflective failed inhibition of reflexive saccades to a visible target. Not all studies support saccadic problems in relatives of patients of schizophrenic cases (de Wilde ea, 2008) or an association with genetic risk rather than disorder status. (MacCabe ea, 2005)

In *backward masking* a target stimulus is presented followed shortly by a 'mask', i.e. a second stimulus. This has the effect of hampering (masking) detection of the target. The interference seems to work backwards in time, hence the name. Schizophrenic individuals find it more difficult than do normals to identify the first (target) stimulus (Del Cul ea, 2006) and this may be due to failure to adequately activate the lateral occipital complex. (Green ea, 2009) Backward masking is also found in some chronic mania patients.

Murray (2002) has suggested that schizophrenic patients are 'developmentally impaired manics', i.e. mania modified by an abnormal brain. Liddle (2001, p. 198) suggests that the essential pathology in schizophrenia is abnormal development of long-distance connections within the brain leading to impaired regulation of modulatory monoamine neurotransmitters; stress then leads to florid psychosis. Frontal projections might normally prevent excessive DA transmission in the basal ganglia during stressful circumstances; if this is not possible, then there may be excessive positive feedback to the cortex that leads to psychosis. Such impaired connectivity might also explain negative and persistent cognitive symptoms. (Liddle, 2001, p. 199) *Neuroimaging*: In general decreased blood flow to the dorsolateral prefrontal cortex correlates with negative symptoms while fronto-temporal abnormalities correlate with positive symptoms including thought disorder (Horn ea, 2009).

Neuroimaging is best confined to the investigation of atypical cases (Lawrie, 2006) and for research. Variations in the type of patients (and control subjects: Blakemore, 2002) employed and their medication status between studies complicate interpretation, as does the state versus trait dilemma. The relative enlargement of the lateral and third ventricles and cortical sulci that is found in some schizophrenics on CT has been deemed by many authors to be static and to represent a neurodevelopmental rather than a neurodegenerative disorder. CT findings also suggest smaller brain volume and length, especially left-sided and in males. (see O'Shea, 1997) In particular, such findings seem independent of duration of psychosis or medication. Young ea (1991) using MRI reported that the normally smaller left amygdala was not a feature of schizophrenia; the latter had an excessively small left parahippocampal gyrus; ventriculomegaly and cerebral atrophy were related to symptom severity; small caudate nuclear heads correlated with severity of negative symptoms; and marked positive symptoms were associated with larger ventriculo-brain ratios (VBR).¹⁰⁵⁸ Twins affected by schizophrenia may have smaller anterior hippocampi than have their co-twins. (Weinberger ea, 1992) Chakos ea (2005) used MRI to examine the hippocampi of young male schizophrenics, older chronic patients, and matched controls. Schizophrenics had relatively smaller hippocampi, more so in chronic cases. Younger patients had larger hippocampi if they were treated with atypical antipsychotics rather than haloperidol. The authors concluded that the hippocampus of male schizophrenics is progressively reduced in size. They also speculated that atypicals might protect against this. Hurlemann ea (2008) found, relative to healthy controls, bilaterally reduced MRI hippocampal volumes in subjects thought to be in a prodromal schizophrenic state; only in those thought to be in the late stages of the prodrome did such reductions correlate with poorer performance on the *Rey Auditory Verbal Learning Test* delayed recall. Schobel ea (2009) used fMRI and found abnormal cerebral blood volume (CBV) increases in the CA1 subfield of the hippocampal formation and the orbitofrontal cortex and abnormal CBV decreases in the dorsolateral prefrontal cortex; baseline CA1 CBV abnormalities predicted progression to psychosis from the prodromal state; CBV in CA1 correlated with psychotic symptoms; and the findings were not influenced by antipsychotic drugs.

Various abnormalities in relaxation times have been reported in MRI studies of schizophrenic subjects, e.g. prolonged T2 values, especially in the left temporal cortex and white matter. Siegel ea (1993) used PET to study unmedicated male schizophrenics and found low metabolic rates in the medial frontal cortical regions and in the basal ganglia; there was loss of the normal lateralisation patterns; and correlations with negative symptoms and group differences (from normal controls) were more prominent in the medial and lateral frontal cortex.

¹⁰⁵⁷ A memory-guides saccade paradigm requires a person to inhibit reflexive saccades and to programme a delayed saccade towards a remembered target.

¹⁰⁵⁸ Increased VBR has also been reported in depressives.

There are many problems of interpretation in neuroimaging studies, e.g., presuming the effects of medication¹⁰⁵⁹, alcohol dependence¹⁰⁶⁰, age¹⁰⁶¹ and sex are controlled for, reports of small structures in chronic cases could mean either progression of atrophy with duration of illness or that smallness predicts chronicity. In their review/perspective, Weinberger and McClure (2002) found that while early CT studies favoured a neurodevelopmental (no progression) for schizophrenia, more recent MRI work suggested neurodegeneration (progression)! They suggest caution in interpreting MRI data: changes could be secondary (adaptive/neuroplastic) to psychosis, MRI changes are so big that we should be finding more gross postmortem changes, and cognitive studies are in general against progression. In fact, most MRI studies that show progressive changes also record clinical improvement!(Weinberger & Marenco, 2003, p. 332)

McDonald ea (2004), using MRI, found that genetic risk for schizophrenia was specifically associated with distributed grey matter volume deficits in bilateral fronto-striato-thalamic and left lateral temporal regions. Genetic risk for bipolar affective disorder was specifically associated with grey matter deficits only in the right anterior cingulate gyrus and ventral striatum. Genetic risk for both disorders was associated with reduced volume of white matter in left frontal and temporo-parietal regions. This was interpreted as representing a common fronto-temporal disconnectivity. Pérez-Iglesias ea (2010a) examined first episode schizophrenia patients and matched controls with diffusion tensor imaging (DTI) and reported that voxelwise analysis revealed four clusters where fractional anisotropy values were significantly lower among the patients; these were localised bilaterally to regions of white matter corresponding to superior and inferior longitudinal fasciculus, forceps major¹⁰⁶², anterior and superior thalamic radiation, and corpus callosum; and the authors concluded that decreased white matter integrity is present early and is localised in fascicle that connect brain regions implicated in schizophrenia. Koch ea (2009) found that schizophrenia was associated with increased fractional anisotropy in corpus callosum, cerebral peduncle, left inferior fronto-occipital fasciculus, anterior thalamic radiation, right posterior corona radiata, middle cerebellar peduncle, and right superior longitudinal fasciculus; increased fractional anisotropy was detectable in inferior sections of the cortico-pontine circuit; and the authors suggest that their findings indicate extended cortical-subcortical changes in white matter integrity in schizophrenia and that their results corroborate earlier work that demonstrated white matter structural deficits in mainly long-ranging association fibres. Pérez-Iglesias ea (2010b) employed DTI and neurocognitive assessment in first-episode schizophrenia patients and found that executive and motor deficits were associated with reduced white matter integrity in the main bundles connecting frontal and temporal cortices and in cortico-subcortical pathways. Because the illness was at an early stage and because medication received was minimal Pérez-Iglesias ea (2010b) felt that such findings were not due to chronicity or treatment. Honea ea (2005) performed a meta-analysis of voxel-based morphometry studies (15 studies, 390 schizophrenic patients, 364 healthy volunteers) and found that the most consistent differences were relative deficits in the left superior temporal gyrus (see Kuroki ea, 2006) and the left medial temporal lobe. Takahashi ea (2009a) used longitudinal MRI (baseline and mean of 1.8 years later) in very high risk people, first episode psychosis cases, and community recruits. Their results suggest progressive gray matter reductions of the superior temporal gyrus during transition to psychosis. However, Takahashi ea (2010), while finding smaller superior temporal gyri on MRI in those at risk of psychosis, found no difference between those who did and those who did not eventually become psychotic.

Various tasks have been used to test brain function. Using the Wisconsin Card Sorting Test (WCST) to activate prefrontal areas, most (e.g. Weinberger ea, 1992) but certainly not all authors have found diminished blood flow in these areas while the task is being performed ('hypofrontality'¹⁰⁶³). The normal reaction to the WCST is an increased blood flow to the DLPFC. According to Molina ea (2005) hypofrontality is easily missed if the patient is assessed whilst at rest and is best performed during an

¹⁰⁵⁹ Sullivan ea(2003) found that atypical, but not typical, drugs were associated with bilateral thalamic volume deficits on MRI. Typical neuroleptics have been associated with larger caudate nuclei, reversing with a switch to atypical drugs.(Jernigan, 2003, p. 57) Lieberman ea(2005) reported that haloperidol, but not olanzapine, were associated with a decrease in grey matter volume in first-episode psychosis.

¹⁰⁶⁰ Sullivan ea(2003) found that comorbid alcohol dependence was associated with pontine deficits. Alcohol dependence on its own was associated with volume deficits in thalamus and pons.

¹⁰⁶¹ Including age of onset.

¹⁰⁶² The occipital radiation of the corpus callosum.

¹⁰⁶³ This has also been described in depressives.

attention task, e.g. in first-episode schizophrenia sufferers. However, Hill *et al.* (2004) in their meta-analytic study found no hypofrontality in first-episode/illness-duration-under-2 years cases but that it became more evident in studies looking at mixed acute and chronic subjects and even more so in chronic patients. Ablation of prefrontal cortex and destruction of dopaminergic (mesocortical) input to the same area produce similar behavioural deficits in animals, and D-amphetamine, an indirect DA agonist, partially alleviates impaired ability to activate prefrontal cortex in patients suffering from schizophrenia. (Liddle, 2001, p. 29) Kellendonk *et al.* (2006) showed that mice that are genetically modified to over-express D2 receptors in the striatum developed problems in working memory and behavioural flexibility. 'Disordered functional connectivity' is a modern term that suggests a possible disruption of interaction between frontal and temporal regions of the brain. Liddle (2001, p. 196) summarised functional imaging studies in schizophrenia and found that, in general and under diverse circumstances, there was a failure to activate the frontal cortex despite adequate engagement in a task; however, during certain tasks (such as paced word generation) the patient can activate the prefrontal cortex (PFC), but there is abnormal co-ordination between PFC and other parts of the brain. Failure to activate the PFC during the WCST appears to be related to low HVA levels in the CSF, suggesting a role for dopaminergic underactivity. (Weinberger *et al.*, 1988) Increased plasma HVA levels during a metabolic stress condition in schizophrenic subjects was interpreted by Marcellis *et al.* (2004) as reflecting an illness-related effect rather than an inherited phenomenon. Blakemore (2002) discussed the evidence for a temporo-frontal disconnection or a dysfunctional cortico-cerebellar circuit in schizophrenia and concluded that whilst the evidence is largely indirect there may be a basis in reality for such findings. Meyer-Lindenberg *et al.* (2005) found evidence for altered hippocampal formation-dorsolateral prefrontal cortex connectivity during working memory activation in schizophrenia. Achim and Lepage (2005) conducted a meta-analysis of 18 studies and found that schizophrenia is associated with abnormal patterns of brain activation during both encoding and retrieval of memories; the prefrontal cortex and hippocampus, amongst other regions, are implicated in the abnormal memory functions. Another meta-analysis (Ragland *et al.*, 2009) found prefrontal activation deficits during episodic encoding and retrieval in patients with schizophrenia. In a meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia published before February 2007 (Minzenberg *et al.*, 2009) found that healthy adults and schizophrenic patients activate similar networks (DLPFC and anterior cingulate cortex [ACC]) but that patients show changed activity with deficits in DLPFC, ACC, and mediodorsal thalamic nucleus; increases in activity in other PFC areas may be attempts to compensate for deficits.

Using diffusion tensor imaging (DTI: MRI), Burns *et al.* (2003) demonstrated reduced white matter tract integrity in the left uncinate and arcuate fasciculi in schizophrenia. Andreone *et al.* (2007) found microstructural disruption of white matter in frontal, temporal and occipital white matter. Skelly *et al.* (2008) reported diffuse deficits in a number of types of white matter tracts and an inverse relationship of DTI fractional anisotropy values with positive symptom scores in association fibres, interpreted as supporting a disconnection explanation for positive symptoms in schizophrenia. Widespread structural dysconnectivity, including the subcortical region, was found in neuroleptics-naive, first-episode, Chinese schizophrenic patients using DTI. (Cheung *et al.*, 2008) Kubicki *et al.* (2008) used DTI and structural MRI in both schizophrenic subjects and controls and found a relative reduction of fractional anisotropy in those parts of the corpus callosum that connect both frontal regions. Friedman *et al.* (2008) used DTI cross-sectionally and found only trend-level lower (than controls) fractional anisotropy (affecting inferior longitudinal fasciculus) in first-episode schizophrenia whereas chronic cases had either significant or trend-level lower fractional anisotropy, suggesting progression. However, the authors admit that their findings will require to be tested by following such cases. Sussmann *et al.* (2009) used DTI and found the same white matter abnormalities¹⁰⁶⁴ in bipolar and schizophrenic patients compared to controls. Kanaan *et al.* (2009), in a relatively large study comprising 76 patients with schizophrenia and 76 matched controls, found widespread clusters of reduced fractional anisotropy affecting most major white matter tracts in patients and these were not associated with duration of illness or duration of treatment. In one study (Kyriakopoulos *et al.*, 2009), adolescent-onset schizophrenia was associated with decreases fractional anisotropy in parietal regions but adult-onset cases also had such decreases in frontal, temporal and cerebellar areas.

¹⁰⁶⁴ Reduced fractional anisotropy in anterior limb of internal capsule, anterior thalamic radiation, and in region of uncinate fasciculus.

Liddle and Pantelis (2003) reviewed brain imaging in schizophrenia and came to the following conclusions: diverse brain areas subtle volume decreases; abnormal gyrification suggests a neurodevelopmental defect but some studies suggest progressive changes; widespread functional (dynamic) dysfunction; abnormal increases and decreases in activities in various areas¹⁰⁶⁵; abnormal connectivity between areas¹⁰⁶⁶; and many inconsistencies in the literature. Therefore, they warn against interpreting individual studies uncritically.

A full listing of neuroimaging findings in schizophrenia (incl. MRS and magnetoencephalography) is beyond the scope of this book. CT scans are now rarely used for research in the area of schizophrenia.

Sample of (mainly recent) neuroimaging findings in schizophrenia

(DL) PFC = (dorsolateral) prefrontal cortex; scz = schizophrenia

Chua and McKenna (1995) reviewed CT, MRI, postmortem and functional imaging studies and concluded that the only well established abnormality in scz was a modest enlargement of the lateral ventricles, with considerable overlap with the normal population.

Lawrie and Abukmeil (1998) reviewed volumetric MRI studies. The 40 relevant studies revealed an overall decrease in whole brain by 3%, temporal lobe by 6% on left and 9.5% on right, and amygdala-hippocampal complex by 6.5% on left and 5.5% on right. There was increased size of the lateral ventricles (44% left, 36% right), being greatest in the body and occipital horns. Segmental studies suggested reduced grey matter and possibly increased white matter. Males had substantially reduced amygdala and hippocampus, with the largest reductions being in the parahippocampus (14% left, 9% right). Few studies gave figures for women only.

Nelson ea (1998) used meta-analysis of MRI studies and found that scz was associated with bilateral smaller (than controls) hippocampi and, probably, amygdala. A systematic review and meta-analysis of MRI studies in first-episode scz patients conducted by Steen ea (2006) whole brain and hippocampal volume are reduced and that ventricular volume is increased relative to healthy controls. Wright ea's (2000) meta-analysis of MRI publications confirmed bilateral reduction in volume of medial temporal lobe structures.

Zakzanis ea (2000) conducted a meta-analysis of CT, MRI, SPECT and PET studies of the temporal lobe in scz. Most cases were normal, a minority had reduced values, and some had increased function and structure rather than a deficit.

Sommer ea's (2001) meta-analysis concluded that overall there is reduced cerebral lateralisation in scz with reduced asymmetry of the planum temporale and the Sylvian fissure, but no reduction in asymmetry of the temporal horn.

Goldstein ea, (2002) in an MRI study, reported that the effects of scz on the brain appear to depend on sex, especially in the cortex (esp. frontomedial cortex, basal forebrain, cingulate and paracingulate gyri, and planum temporale); the normal asymmetry of the planum was disrupted in men and women with scz. In other words, factors producing sexual brain differences may modulate insults causing scz.

Neither duration of illness or MRI measures showed any significant relationship to treatment responsiveness in the paper by Robinson ea.(1999)

In a two-year follow-up MRI study in scz, Westmoreland ea (1999) found that the basal ganglia became bigger with typical neuroleptic use (see also Navari & Dazzan, 2009), but smaller with atypical drug use. This has been demonstrated by Scheepers ea (2001) for clozapine responders (but not for non-responders).

Reduction in volume of white matter near left fronto-occipital fasciculus on follow up of patients who developed (retrospectively) frank psychosis.(Walterfang ea, 2008)

Using a combination of PET (¹⁸F-fluorodeoxyglucose), MRI and a spatial attention test in never-medicated scz (8 m, 5 f, mean age 28.5 years) and normal volunteers, Lehrer ea (2005) found that the patients had diminished glucose metabolism in the medial dorsal nucleus, posterior thalamus, and prefrontal cortex, interpreted as reflecting deficits in interactions between frontal executive areas and thalamic sensory and association processes.

PET study found dopamine overactivity during scz prodrome (especially in associative striatum) that correlated with symptom severity and neurocognitive dysfunction.(Howes ea, 2009)

In a meta-analysis of 25 MRI studies, Boos ea (2007) found that first-degree relatives of scz patients (compared to normal controls) had smaller hippocampi, less grey matter, and larger third ventricles.

Unaffected relatives of patients with scz had significantly larger pituitary volumes on MRI compared to controls; the pituitary was even bigger in relatives of patients with familial scz; there was no significant difference between relatives of bipolar patients and controls; and, patients with scz had relatively large pituitary if receiving antipsychotic drugs that increase prolactin.(Mondelli ea, 2008)

MRI of first-episode and chronic scz (meta-analysis of 27 articles): both groups had grey matter reductions in thalamus, left uncus/amygdala region, insula bilaterally, and anterior cingulate; only in first-episode cases were there decreases in grey matter in both caudate heads; and decreases in cortical regions were more widespread in chronic cases.(Ellison-Wright ea, 2008)

MRI of first-episode, antipsychotic-naïve scz patients found volume loss in right superior and middle temporal gyri and right anterior cingulate gyrus; functional networks involving right superior and middle temporal gyri were associated with symptom severity.(Lui ea, 2009)

New episode psychosis (mostly scz) treated for 3-4 weeks with antipsychotic medication was associated with enlarged (by 10%) caudate nuclei bilaterally.(Chua ea, 2009)¹⁰⁶⁷

¹⁰⁶⁵ Frontal and medial temporal, basal ganglia, thalamic.

¹⁰⁶⁶ Possibly involving long myelinated axons as well as synapses and dendrites.

¹⁰⁶⁷ These were compared with first episode psychosis (again mainly schizophrenia). Note that in another study that first-episode cases had decreases in grey matter in both caudate heads.(Ellison-Wright ea, 2008)

Longitudinal MRI of 35 ultra-high risk for psychosis cases of whom 12 experienced psychosis (converters) by 12 months follow-up found significantly greater brain contraction (cortical volume loss) in right prefrontal region in converters.(Sun ea, 2009)

Patients with scz fail to activate and to deactivate anterior prefrontal/anterior cingulate cortex (part of 'default mode network' involved in maintain sense of 'self') on fMRI during performance of a working memory task.(Pomarol-Clotet ea, 2008)

Compared with controls, people with scz or schizoaffective disorder marked prefrontal and temporal cortical thinning (on MRI), regardless of age, and this is independent of medication.(Nesvåg ea, 2008)

Authors compared cortical thickness in normals, scz patients, and unaffected siblings with MRI and and calculated heritability: patients had widespread thinning (mainly frontal and temporal) but unaffected siblings did not differ significantly from normal controls, arguing against cortical thickness being an intermediate phenotype for scz.(Goldman ea, 2009)

Patients with scz had reduced grey matter volume on MRI in middle and inferior frontal gyri, the inferior frontal gyri volume also being reduced in unaffected siblings.(Harms ea, 2010)

Pajonk ea (2010) found that hippocampal volume (MRI) increased in scz patients and in healthy controls after 3 months of cycling (aerobic exercise) but not in a non-exercise group; short-term memory improved if hippocampal volume increased; the patients (but not controls) who hippocampi increased in size showed (MRS) an increase in hippocampal N-acetylaspartate to creatine ratio.

Cross-sectional comparison using fMRI of prodromal symptoms ('at-risk'), first-episode schizophreniform psychosis, and healthy volunteers during an overt verbal fluency task and an N-back working memory task: activation was intermediate in 'at-risk' group relative to the 2 other groups in inferior frontal and anterior cingulate cortex during verbal fluency task and in inferior frontal, dorsolateral prefrontal and parietal cortex during working memory task.(Broome ea, 2009)

Using fMRI (while listening to mixtures of urban noise, i.e white noise) and testing P50 evoked response to paired-click sensory gating task, outpatients with scz showed greater activation than controls of hippocampus, thalamus, and prefrontal cortex (PFC) and evoked responses correlated with haemodynamic responses in hippocampus and PFC; such findings suggest involvement of these areas in gating deficits.(Tregellas ea, 2009b)

Stroop test during fMRI in scz (and controls) showed significant attenuation of activity in anterior cingulate gyrus, left pre-/postcentral gyrus and left inferior frontal junction (LIFJ); at follow-up there was a significant increase in activation in LIFJ associated with reduction in positive symptoms, suggesting that LIFJ is important in development of positive symptoms.(Krabbendam ea, 2009)

Drug-naive and drug-free scz patients and matched controls underwent fMRI to look at neural responses to feedback of successful and unsuccessful monetary gain or avoidance of loss; functional connectivity was assessed between medial prefrontal cortex (MPFC) and ventral striatum (VS), areas known to be activated by feedback of reward and loss; results suggested differential impairment and reduced connectivity between MPFC and VS.(Schlagenhauf ea, 2009)

Immediate contextual signals do not sufficiently bias the caudal lateral PFC activity needed to to select appropriate behavioural representation in patients with scz (MRI) and, to compensate, patients inefficiently use temporal episodic information through higher activation in rostral lateral PFC regions.(Barbalat ea, 2009)

Using fMRI and Hayling sentence completion test, Whalley ea (2009) found that unmedicated subjects at high genetic risk for scz developed activation increases in left middle temporal gyrus when they developed symptoms.

In a controlled PET (¹⁸F) study involving facial emotion recognition, it was found that right-handed non-acute patients with scz showed left amygdala hyperactivation in both emotional and control tasks and the right amygdala showed no differential activation in any of the tasks: scz is associated with non-task specific amygdalar hyperactivation during a continuous emotional and non-emotional task compared to healthy controls.(Fernandez-Egea ea, 2009)

Non-psychotic offspring of patients with scz have relatively small caudate nuclei bilaterally.(Rajarethinam ea, 2007)

MRI study in first episode scz showed that cognitive deficits are related to brain volume abnormalities in inferior parts of DLPFC.(Minatogawa-Chang ea, 2009)

At baseline MRI, adolescent offspring of scz parents showed decreased gyral surface area in fronto-parietal lobes and increased sulcal curvature and parietal gyral cortical thinning compared to healthy subjects; after a year there were shrinkage of total surface area in bilateral frontal and occipital regions and preservation of cortical thickness whereas controls had preserved or increased surface area and cortical thinning; the findings led Prasad ea (2010) to suggest that they were observing a divergent neurodevelopment trajectory and they suggested that cortical surface measures may be more sensitive to genetic liability to scz compared to volume measures.

In a controlled fMRI study of scz, Henseler ea (2009) looked at 3 brain systems underlying maintenance-related subprocesses of working memory: patients showed less activation of fronto-opercular, intraparietal and anterior cingulate cortex during non-articulatory maintenance of phonological information as well as attenuated hippocampal deactivation, and prefrontal activation depended critically on current symptom status; during visuospatial maintenance patients had impaired activation of superior parietal, temporal and occipital cortex, and increased activation of frontal eye fields and inferior parietal cortex; and activation was normal during articulatory rehearsal task.

Low IQ subjects at increased risk for scz differed on MRI from low IQ subjects without this risk – reduced amygdala volume in the former may be associated with negative symptoms.(Welch ea, 2010)

Ultra-high risk (UHR) subjects who transition to psychosis (UHR-P) had reduced fractional anisotropy (FA) bilaterally in medial frontal lobes and, compared to those not becoming psychotic (UHR-NP), had lower FA lateral to right putamen and in left superior temporal lobe and they increased FA in left medial temporal lobe; among UHR-P positive PANSS negatively correlated to FA in left middle temporal lobe; among all UHR positive PANSS negatively correlated to FA in right superior temporal lobe.(Bloemen ea, 2010)

Using an affective face recognition paradigm and fMRI Satterthwaite ea (2010) found that patients with scz performed slowly; comparison subjects recruited expected cortical areas more than did patients, and more severely symptomatic patients showed relatively diminished recruitment; increased symptoms correlated with excess amygdala and orbitofrontal cortex response to threatening faces; and comparison subjects showed a negative relationship between amygdala and cortical areas involved in cognition, while patients exhibited weakening of this relationship: i.e. the limbic system is over responsive and the cortical facial recognition memory response is decreased.

Patients with auditory hallucinations (AH) have reduced interhemispheric connectivity in both primary and secondary auditory cortices on fMRI compared to both non-AH patients and healthy controls whilst passively listening to words.(Gavrilescu ea, 2010)

Prata ea (2009) examined the effect of a polymorphism in the dopamine transporter gene (variable number of tandem repeats in 3' untranslated region) on brain function in scz patients and healthy comparison subjects: variations in the dopamine transporter gene normally modulates insular, cingulate and striatal function but its effect on activation in DLPFC is altered in scz.

PET after pharmacological depletion in untreated scz patients and healthy controls showed a larger increase in associative striatum D2 receptor availability in the former group (suggesting increased synaptic dopamine concentration), especially in pre-commissural dorsal caudate, and no differences were found between the two groups in the limbic and sensorimotor striatum: absence of group differences in limbic striatum questions the therapeutic importance of mesolimbic selectivity of 'atypical' antipsychotics.(Kegeles ea, 2010)

PET and fMRI and working memory task in outpatients with prodromal signs of psychosis showed direct correlations between altered PFC function and subcortical DA synthesis capacity.(Fusar-Poli ea, 2010)

MRS studies (see O'Shea, 1997 for an introduction) reported reduced levels of membrane phospholipids at all stages of scz and increased breakdown products of membrane phospholipids in the early drug naïve patient; a reduction in signal intensity in the hippocampal region and the DLPFC; increased glutamine levels in medial prefrontal cortex in neuroleptic-naïve patients, probably due to diminished glutamatergic activity locally; a gross deficit in cortical grey matter; both early- and adult-onset scz patients have less than normal regional N-acetylaspartate (NAA) relative signals, suggesting neuronal damage or malfunction in the hippocampi and DLPFC; first episode drug-naïve Japanese scz sufferers had disturbed membrane phospholipid metabolism in both temporal lobes and reduced energy demands in the left temporal lobe; DS patients have lower ratios of NAA to creatinine plus phosphocreatine than healthy controls of non-deficit cases, suggesting neuronal loss in medial prefrontal cortex in deficit cases; decreased NAA in both (medio-dorsal) thalami in male scz patients but not in healthy males; first degree relatives of scz sufferers compared to controls had greater phospholipid breakdown, even in youth; lower prefrontal NAA predicted more severe negative symptoms; and mainly left-sided NAA reduction in scz. Jensen ea (2002), using a small sample of chronic, medicated patients, confirmed altered membrane phospholipid metabolism in all regions implicated in scz. Bustillo ea (2002) found high choline levels in the caudate nucleus in scz that could not be due to medication.

Flycht ea (2001) looked at *skin fibroblasts* and tyrosine transport across cell membranes in first-episode and chronic scz: lower maximal transport capacity (Vmax) and affinity of tyrosine binding sites (Km) were compatible with a cell membrane disturbance; and, as changes were transmitted through several cell generations of cultured fibroblasts, it was interpreted as a genetic trait.

Patients with scz showed deficits in hippocampal activation during a memory task compared to bipolar patients (Hall ea, 2010) and there were differences in PFC activation between the two diagnostic groups.

Water intoxication: Many psychotic patients, especially those with schizophrenia, drink excessive fluids. This might possibly be based either on delusional beliefs or on an inappropriate ADH secretion (SIADH). Polydipsic chronic schizophrenics may have less suppression of cortisol in the DST test, although depressed schizophrenics may have a particularly low rate of non-suppression of cortisol in response to dexamethasone.(Q.V.) Perhaps hypothalamic dysfunction causes both polydipsia and cortisol dysregulation. Water intoxication can be fatal and primary polydipsia (no medical cause) in psychiatric patients foreshortens life.(Hawken ea, 2009). The early features of the condition are headache, blurred vision, polyuria, vomiting, tremor, and a worsening of the psychosis. More severe manifestations are muscle cramps, ataxia, delirium, stupor, coma and convulsions. Various treatments have been advocated, such as frusemide, urea, or water restriction. Incidentally, there is a report of an exaggerated ACTH response to acute metabolic stress exposure in the form of 2-deoxy-D-glucose in schizophrenia.(Elman ea, 1998)

Transmethylation hypothesis: This old theory holds that schizophrenia may be due to an excess of methylated biogenic amines. DMT (dimethyltryptamine), for example, was used on Haiti to induce mystical states. It is taken as a snuff. DMT by injection causes a transient schizophrenia-like psychosis. Mescaline is a methylated substance chemically related to dopamine and noradrenaline (NA). Its effects do not closely resemble schizophrenia. LSD is a methylated derivative of indoleamine. Methionine, a methyl donor, appears to exacerbate schizophrenic symptoms. It is possible that all one is seeing here is a toxic state superimposed on chronic schizophrenia.

Many, but not all, reports suggest low values for *platelet MAO* in schizophrenia. This finding has been reported in other psychiatric disorders, and neuroleptic drugs can produce this effect. Should the findings be relevant, they could have relevance for the transmethylation and dopamine hypotheses. Less MAO could result in excess monoamines or their abnormal metabolites becoming available.

*Carbonyl stress*¹⁰⁶⁸: Glyoxalase 1 (involved in detoxification of reactive carbonyl compounds) deficits and carbonyl stress may have a role in the pathogenesis of some cases of schizophrenia.(Arai ea, 2010)

*Dopamine*¹⁰⁶⁹: The dopamine hypothesis has been reviewed by O'Shea (1997) and Moncrieff¹⁰⁷⁰ (2009). Typical antipsychotics all block D2 receptors. The alpha isomer of flupenthixol blocks dopamine receptors

¹⁰⁶⁸ Accumulation of advanced glycation products (e.g. pentosidine) follow carbonyl stress, a situation involving an increase in reactive carbonyl compounds and their attendant protein modifications; vitamin B6 detoxifies reactive carbonyl compounds. A carbonyl group consists of a carbon atom double-bonded to an oxygen atom: C=O.

(equally blocks both D1 and D2) and is therapeutic in schizophrenia; the beta isomer does not block dopamine receptors and has no such therapeutic value. (Johnstone *et al.*, 1978) Selective/preferential D2 antagonism (e.g. sulpiride, haloperidol) work as well as non-selective agents¹⁰⁷¹. (Seeman, 1980) However, the degree of DA receptor blockade as assessed by PET does not distinguish neuroleptic responders from non-responders. Connell, in 1958, described amphetamine psychosis, a condition thought to resemble paranoid schizophrenia. However, amphetamine psychosis is characterised by over-responsiveness rather than emotional blunting, thought disorder is rare, and tactile and olfactory hallucinations are more common than in schizophrenia. In one study of healthy individuals, (Krystal *et al.*, 2005) ketamine and amphetamine produced positive symptoms and euphoria, but perceptual changes¹⁰⁷² were caused only by ketamine whereas only amphetamine caused hostility, grandiosity, and somatic concern; both drugs produced conceptual disorganisation but only ketamine induced concrete thinking and strange mannerisms. A reduction in circulating plasma levels of homovanillic acid¹⁰⁷³ over a period of weeks that correlates with clinical response to antipsychotic drugs can be interpreted as being in favour of a role for dopamine in schizophrenia in particular, psychosis in general, or simply as something that these drugs do. Increased interleukin-2 (which increases DA neurotransmission) in the CSF of neuroleptic-free schizophrenics, has been reported. Amphetamines also exacerbate true schizophrenia, even if the patient is compliant with his medication. (Curran *et al.*, 2004) Amphetamine challenge leads to greater release of DA in schizophrenic patients than in healthy controls. (Laruelle *et al.*, 1999) This may represent a mechanism whereby stress leads to excess DA release in schizophrenia. (Stefan *et al.*, 2002, p. 61) PET and SPECT studies have not consistently demonstrated increased numbers of D2 receptors in drug-naïve schizophrenia. Also, efforts to link schizophrenia with the D2 dopamine receptor gene region of chromosome 11 have mostly failed. The same applies to the D3 receptor gene. Seeman *et al.* (1993) found the D4 receptor increased in schizophrenic's brains. Nevertheless, SPECT and PET studies suggest that D2 receptors may be overactive in some cases of schizophrenia, particularly during periods of psychosis, and such cases may be more likely to respond best to antipsychotic drugs. Hirvonen *et al.* (2005) based on twin studies, have suggested that D2 receptor upregulation in the caudate is related to genetic risk for schizophrenia.

Methamphetamine users who become psychotic tend to have a familial tendency to develop schizophrenia and are more likely to have schizotypal features during childhood; also, these two factors determine duration of psychosis. (Chen *et al.*, 2003)

One modern reformulation of the dopamine hypothesis reads as follows: negative symptoms are due to hypodopaminergic activity in the mesocortical system, and positive symptoms are a consequence of hyperdopaminergic activity in the mesolimbic system¹⁰⁷⁴. It has been suggested that positive symptoms are 'release phenomena' in the Jacksonian sense. Put another way, there may be increased D2 and D4 activity in the limbic system and increased 5-HT₂ and reduced DA activity in the frontal area and all of these may be reversed by atypical neuroleptics.¹⁰⁷⁵ Animal work suggest that 5-HT₂ blockade could increase DA activity in the frontal cortex. (Kapur & Remington, 1996) Perhaps DA may exert its malign effects during

¹⁰⁶⁹ Dopamine is needed for many reasons, including attaching **salience** (and hence paying attention) to things, for reward (pleasure), and to prevent Parkinson's disease. Kapur (2003) suggested that mesolimbic DA gave meaning/salience to external stimuli and inner thoughts and that excess DA release in psychosis causes otherwise insignificant events to be imbued with great significance, e.g. a trivial remark by a radio announcer about the weather becomes a personal comment about the patient. According to Murray (2008) excess DA leads to aberrant assignment of salience (imbues events with significance) to external and internal stimuli: 'birds sing more loudly, flowers are of a deeper colour, I must be more important, strange things are afoot, a battle between Good and Evil is going on', etc. Excess DA (increased synthesis, release, or D2 receptor occupancy) leads to an increase in the positive symptoms of psychosis. Murray (2008) states that there is increased DA synthesis in the caudate and putamen of both prodromal cases of psychosis and in patients' relatives compared to controls.

¹⁰⁷⁰ Moncrieff (2009) is highly critical of the hypothesis: the results are contradictory; antipsychotics may reduce symptom severity simply by causing neurological suppression; post-mortem findings (DA and DA receptors, HVA) are negative or inconclusive; prior medication may influence some results; and confounding factors (e.g. movement, arousal, attention, stress, and smoking) are rarely studied.

¹⁰⁷¹ Block D1 and D2: e.g. flupenthixol, fluphenazine.

¹⁰⁷² Ketamine produced perceptual distortions but not hallucinations in another study of healthy volunteers. (Pomarol-Clotet *et al.*, 2006)

¹⁰⁷³ The major DA metabolite.

¹⁰⁷⁴ One version has it that reduced prefrontal DA, itself a product of preexisting prefrontal pathology, causes upregulation of subcortical DA activity leading to psychosis. Rodent prenatal lesion studies suggest that release of excess DA may be delayed until adulthood. (Laurelle, 2003, pp. 376 and 378)

¹⁰⁷⁵ It should be noted that haloperidol has a higher affinity for D4 receptors than does clozapine, and D4-selective drugs have not demonstrated antipsychotic activity.

adolescence by affecting the balance of excitatory and inhibitory inputs to cortical pyramidal cells or by influencing cortical information processing around the time of puberty.(Lewis, 1997)

One formulation of the DA hypothesis is illustrated in the box.

Dopamine and schizophrenia (VTA = ventral tegmental area)

Genes and/or prenatal insults to mesocortical pathway

↓

Decrease in DA in cortex, especially in frontal areas

↓

Loss of cortico-limbic glutaminergic transmission *and* loss of inhibitory feedback of VTA by cortex

↓

Loss of inhibition of mesolimbic system

↓

Increased mesolimbic DA transmission

Notes: It has been suggested that clozapine reduces negative symptoms by blocking 5-HT with a resulting increase in DA in the mesocortical system. Phencyclidine given to monkeys reduces DA turnover and clozapine then normalises dopaminergic turnover in the prefrontal cortex.(Elsworth ea, 2008)

The dopamine hypothesis fits less well for clozapine¹⁰⁷⁶ than for the older, 'typical' agents. Interestingly, amphetamine challenge has been noted to improve cognitive functioning in schizotypy without affecting other symptoms of psychosis.(Maier ea, 1999; O'Flynn ea, 2003, p. 92)

Overall, many linkage studies have been performed but there is no definite linkage between schizophrenia and any DA receptor.

It is commonly believed that antipsychotic drugs produce a delayed response in schizophrenic patients but it is probably truer to say that the response is a progressive one.(e.g. Agid ea, 2003)

Serotonin: The activity of 5-HT₂ cortical receptors decreases with age. The 5-HT partial agonist m-CPP exacerbates the positive symptoms of schizophrenia. Serotonin modifies DA release.

PCP induces symptoms resembling negative and positive schizophrenic symptoms¹⁰⁷⁷. The latter is accompanied by decreased dopaminergic terminal activity in the frontal cortex that can be normalised by giving 5-HT₂ antagonists. Therefore, 5-HT₂ antagonism indirectly activates midbrain dopaminergic activity and increased DA release in frontal cortex. Using a combination of 5-HT₂ and DA receptor antagonists causes selective enhancement in prefrontal cortex with resulting correction of the regional imbalance between cortical and midbrain dopaminergic mechanisms. 5-HT₂ antagonism may at least partly explain the beneficial effects of clozapine on negative symptoms¹⁰⁷⁸. The addition of an SSRI to an antipsychotic drug may improve negative symptoms and various mechanisms have been proposed as to how this might happen¹⁰⁷⁹.(Chertkow ea, 2009) Addition of the 5-HT_{1A} partial agonist to atypical antipsychotics in patients with schizophrenia or schizoaffective disorder led to no improvement in either cognition or symptoms¹⁰⁸⁰.(Piškulic ea, 2009)

Schizophrenics who never received neuroleptics or who did not receive them in the recent past show no difference from controls of similar age in 5-HT₂ receptor status on PET scanning.(Lewis ea, 1999)

Neuroleptic-naïve schizophrenics have reduced 5-HT_{2A} receptors in the parietal and frontal cortex on PET.(Ngan ea, 2000; Rasmussen ea, 2010)

Glutamate: According to Carlsson (1988), healthy mesolimbic glutaminergic neurones inhibit the mesolimbic dopaminergic pathways. PCP, a non-competitive inhibitor of NMDA receptor-mediated

¹⁰⁷⁶ Aripiprazole is a partial agonist at D₂ receptors.

¹⁰⁷⁷ Additionally, McCarron ea (1981) described a catatonia-like syndrome with PCP.

¹⁰⁷⁸ The blood-brain barrier may hold the key to the superiority of clozapine. **P-glycoprotein** (Pgp) is a drug efflux transporter. It binds most antipsychotic drugs as well as certain anti-cancer drugs and antibiotics. Oncologists know that inhibition of Pgp can reverse multi-drug resistance in malignant cells. Clozapine is relatively independent of transport by Pgp, which may at least partly explain its effectiveness in drug-resistant schizophrenia.(Loscher & Potschka, 2005)

¹⁰⁷⁹ I.e. 5-HT receptors, tyrosine hydroxylase, glutamate decarboxylase 67, protein kinase C beta, receptor for activated C-kinase 1 (Rack 1), various transcription and neuroprotective factors, calcium signalling, and cytokine receptors for IL-8 and chemokines. The present author was introduced to the augmentation of antipsychotic drugs with clomipramine for negative symptoms by the late Dr Aidan J McGennis at St Brendan's Hospital, Dublin, in 1981!

¹⁰⁸⁰ This 6-week study of chronic patients might have been too short **or** intrinsic 5-HT_{1A} receptor activation by atypical drugs might have interfered with the effects of the putative augmenting agent.

transmission, may block this controlling effect. Ketamine, an NMDA receptor antagonist, may produce thought disorder similar to that found in schizophrenia when employed in subanaesthetic dosage. Drugs potentiating dopaminergic activity may induce or exacerbate schizophrenic activity.

Glutamate in schizophrenia

- Specific loss of mRNA that encodes for non-NMDA glutamate receptors reported in hippocampi of schizophrenic patients (Harrison ea, 1991) - authors suggested this might be due to reduced glutamate production
- Théberge ea (2007) looked at never-treated first-episode schizophrenic patients and found increased glutamate levels in anterior cingulate and thalamus; thalamic glutamate was significantly decreased after 30 months; some grey matter reductions seen at 10 months, becoming widespread at 30 months; parietal and temporal lobe grey matter loss correlated with loss of thalamic glutamate; authors speculate about neurodegeneration or plastic response to decreased subcortical activity
- In mice, a reduction in glutaminase¹⁰⁸¹ may have antipsychotic-like properties (Gaisler-Salomon ea, 2009)

Neuroleptics may increase glutamatergic activity. Complexins I and II are markers for inhibitory and excitatory neurones respectively. They are presynaptic proteins involved in the fusion of storage vesicles with cell membranes. There is early evidence of an excessive loss of complexin II in the medial temporal lobe in schizophrenia.(Harrison & Eastwood, 1998) D-cycloserine is a partial agonist at the glycine modulatory site of NMDA receptors and might improve negative symptoms in schizophrenia, as might the adjuvant use of glycine.(Heressco-Levy ea, 2002) These substances may have the opposite effect, an increase in negative symptoms, when added to clozapine! Hashimoto ea (2003), using high-performance liquid chromatography, found significantly lower serum levels of D-serine in schizophrenia than in controls. Neeman ea (2005) found plasma glycine levels and glycine-serine ratios were lower and homocysteine levels were higher in schizophrenia than in normals, low glycine levels correlating with more negative symptoms. Buchanan ea (2007)¹⁰⁸² found no significant difference between placebo and either glycine or D-cycloserine in terms of change in negative or cognitive symptoms of schizophrenia. Elevated maternal homocysteine levels in the third trimester increases risk for schizophrenia in offspring at least two-fold.(Brown ea, 2007) According to Lane ea,(2005) N-methylglycerine (sarcosine), a potent endogenous inhibitor of glycine transporter 1 (Gly T-1), added to stable atipsychotic drug regimens, may improve negative and cognitive symptoms of stable chronic schizophrenia; D-serine¹⁰⁸³ and sarcosine can improve positive symptoms in chronic schizophrenic cases on stable antipsychotic drug regimens; and sarcosine (more than D-serine) may also benefit acutely ill patients with schizophrenia when added to antipsychotic drug treatment.

LY2140023¹⁰⁸⁴ is a highly selective agonist at group II metabotropic glutamate receptors¹⁰⁸⁵ and no significant affinity for dopamine receptors. There is preliminary evidence that LY2140023 has antipsychotic activity.(Patil ea, 2007)

Hypoxia seems to render neurones susceptible to glutamate-induced damage. Early damage of this sort might cause schizophrenia in adolescence or later when abnormal circuitry comes under increased cortical control with resultant increased dopamine activity. Alternatively, the original hypoxia/glutamate insult reduces NMDA receptor availability with diminished inhibitory modulation via glutamate-dependent GABA activity, causing over stimulation of certain brain pathways.

Gao ea (2000), using in situ hybridisation, reported a decrease in the NR1 subtype of the NMDA receptor in the hippocampus. There is no evidence of an association between schizophrenia and the 2664C/T polymorphism of the NR2B subunit (of NMDA) gene. According to Owen ea,(2005) the genes likely to be

¹⁰⁸¹ Synaptic glutamate is chiefly taken up by the surrounding astrocytes and converted into glutamine by glutamine synthetase. The glutamine is then taken up by neurones and converted back into glutamate by **glutaminase**. Glutaminase-deficient mice display parahippocampal hypoactivity, insensitivity to pro-psychotic drugs and potentiated latent inhibition.

¹⁰⁸² This was a 16-week multi-site, double blind, double-dummy, parallel group, randomised trial of adjunctive glycine, D-cycloserine, or placebo.

¹⁰⁸³ Full agonists at glycine site of NMDA receptor include D-serine, D-cycloserine being a partial agonist.

¹⁰⁸⁴ A pro-drug that is metabolised to the active compound (but low bioavailable) LY404039.

¹⁰⁸⁵ Made up of mGluR2 and mGluR3.

involved in schizophrenia code for proteins that may impact, in one way or another, on glutamate receptor function: dysbindin-1, neuregulin-1, D-amino acid oxidase and its activator DAOA, and regulator of G protein signalling 4. It is possible that changes in cortical glutamatergic transmission lead to dopaminergic changes as a secondary phenomenon, but, as the authors admit, the truth is often more complicated than any simple theory. Neuregulin-1 (at chromosome 8p) is highly expressed in brain and signals through tyrosine kinase receptors, thereby being involved in neurodevelopment. Neuregulin-1¹⁰⁸⁶ seems to play a role in influencing susceptibility to schizophrenia and bipolar disorder,(Green ea, 2005) although not all studies are positive.(Duan ea, 2005) There may be an association of neuregulin-1 with schizotypal personality.(Lin ea, 2005)

The resemblance of phencyclidine psychosis to schizophrenia has been questioned.(O'Shea, 2000b)
GABA: Akbarian ea (1995) found a pronounced reduction in glutamic acid decarboxylase (a key enzyme in GABA synthesis) mRNA levels in schizophrenic prefrontal cortex (PFC) in the absence of significant cell loss. Others have confirmed this finding. It did not seem to be a treatment effect. Maldonado-Avilés ea (2009) found lower levels of mRNA for the delta subunit¹⁰⁸⁷ of the GABA-A receptor in the dorsolateral prefrontal cortex in schizophrenia and suggested that this may contribute to deficient tonic inhibition and prefrontal cortical dysfunction. The density of chandelier neurone axon terminals¹⁰⁸⁸ immunoreactive for the GABA membrane transporter (GAT-1) is reduced in most patients with schizophrenia. There may be down-regulation of glycoproteins secreted preferentially by cortical GABAergic prefrontal neurones in schizophrenia and psychotic bipolar affective disorder. Treatment of chronic schizophrenia with MK-0777¹⁰⁸⁹, a benzodiazepine-like drug undergoing trials for the treatment of anxiety showed some promise in alleviating cognitive deficits.(Lewis ea, 2008)

The reader is referred to the hippocampal glutamic acid decarboxylase (GAD) mRNA study of Heckers ea.(2002)

*Acetylcholine*¹⁰⁹⁰: Acetylcholine is important in cognition. Lieberman ea (2008) point out that muscarinic and nicotinic receptor numbers may be reduced in schizophrenia, that a functional polymorphism of the alpha-7 nicotinic receptor has been linked to this condition, that acetylcholine modulates striatal and cortical dopamine, that people with schizophrenia smoke heavily, and that clozapine's muscarinic receptor agonism may be important for its effects on positive and negative symptoms. Xanomeline is an M1 and M4 agonist and M5 antagonist but it also has other agonist (5-HT_{1A} and 1_B) and antagonist (5HT₂) properties. It may have a role in improving verbal learning and short term memory in schizophrenia.(Shekhar ea, 2008) DMXB-A is a cholinergic nicotinic partial agonist for the alpha-7 receptor that may improve negative symptoms.(Freedman ea, 2008)

*Free radicals*¹⁰⁹¹: Enzymes such as superoxide dismutase and other substances¹⁰⁹² defend against oxidative injury. Caloric restriction reduces injury from oxygen free radicals. Starvation, heavy cigarette smoking, and excess alcohol consumption all increase oxidative tone with the production of oxyradicals. Studies suggest that oxidative injury may be present at the start of non-affective psychosis, whether or not the patient has received antipsychotic drugs. Vitamins E and C supplements and fats from fish or vegetables rather than from animals or birds may be of some protection.(Mukherjee & Mahadik, 1997) However, there is some animal work suggesting that nicotine may be neuroprotective (Belluardo ea, 2000) and Zammit ea,(2003b) looking at Swedish conscripts, found that cigarette smoking at ages 18-20 was associated with a lower rate of developing schizophrenia!¹⁰⁹³

¹⁰⁸⁶ With its gene on 8p12. Dysbindin (6p) may play a similar role.(Breen ea, 2006)

¹⁰⁸⁷ This was unrelated to medication use, whereas alpha-4 levels were related to medication at time of death.

¹⁰⁸⁸ Called cartridges: these distinctive arrays of axon terminals provide inhibitory input to the initial axonal segment of pyramidal cells.

¹⁰⁸⁹ MK-0777 has selective activity at GABA-A receptors containing alpha-2 or alpha-3 subunits.

¹⁰⁹⁰ See also smoking.

¹⁰⁹¹ These are chemical species with an unpaired electron in one of their orbits. The most toxic is the hydroxyl ion.

¹⁰⁹² Examples are urate, glutathione, vitamins E and C, β-carotene, and quinones. Glutathione is important in the phospholipid pathway and there has been some benefit from giving the glutathione precursor **N-acetyl-cysteine** adjunctively to people with schizophrenia.(Berk ea, 2008) N-acetyl-cysteine is the specific antidote for paracetamol: a toxic breakdown product of paracetamol is scavenged by glutathione and when the body runs out of glutathione, as in common in the alcoholic, the paracetamol metabolite attaches itself to liver cells and kills them.

¹⁰⁹³ However, this study only had data on exposure and confounders for one point in time, i.e. commencement or cessation of smoking after conscription was not controlled for.

Heat shock proteins: Heat shock proteins may be involved in various neuroprotective mechanisms. There is some evidence that antibodies to these proteins are increased in schizophrenia. (Schwarz ea, 1999)

Viruses: Are patients with schizophrenia genetically predisposed to infection? Do the peaks of schizophrenic births in winter and early summer increase the likelihood of an infectious aetiology? In a 25-year-long Russian study of a block of flats, using uncertain diagnostic criteria, there did appear to be some evidence for a 'spread' of schizophrenia! Viruses may alter cell function without killing the cell.

*Viruses and other infectious agents*¹⁰⁹⁴

Leask ea (2002) - data from UK National Child Development Study – unable to implicate common childhood viral illnesses in aetiology of adult psychotic illness.

Against horizontal transmission of schizophrenia: Cooper ea (1987) - no greater an incidence of schizophrenia in psychiatric nurses 1955-1979 than in general nurses during same period

Mednick ea (1987) - rates of schizophrenia in young adults exposed during foetal life to influenza epidemic in Helsinki in 1957 - those exposed during *second trimesters* had increased risk of later schizophrenia

Similar findings reported in the northern and southern hemispheres in some (e.g. Sham ea, 1992) but not all (e.g. Crow & Done, 1992) studies (see O'Shea, 1997)

Interferon levels failed to distinguish between FES and healthy controls (Becker ea, 1990)

Brown ea (2004): significant association between maternal interleukin-8 level during second trimester and risk of schizophrenia spectrum disorders in offspring.

Brown ea (2004): used archived maternal serum assayed for influenza antibody in pregnancies - risk of schizophrenia in offspring 7-fold for exposure during *first trimester*, with no increased risk for exposure at other pregnancy stages

Brown AS ea (2000): rubella exposure during first trimester may be a factor in some non-affective psychoses

O'Callaghan (2001): other suggested viruses that might have a role in schizophrenia include Borna disease virus, the cause of 'crazy disease' (equine encephalitis) and retroviruses

Rasmussen ea (2006): a common non-functional allele of the CCR5 gene with deletion of 32-bp segment in open reading frame confers resistance to infections with macrophage-infecting strains of HIV, and there is some evidence that this deletion may be a susceptibility factor in late-onset schizophrenia

Dickerson ea (2003a): serological evidence of herpes simplex type 1 infection independently predicted cognitive dysfunction in people with schizophrenia

Jablensky (2003, p. 219) - arguing that having older siblings increases risk of developing schizophrenia may be explained in many ways, e.g. children bringing viruses into the home, sample/statistical artefact, or a birth order effect - PCR has not revealed viral nucleic acids to suggest a persistent or latent viral infection - retrospective recall correlates extremely poorly with serology

Dickerson ea (2003b): valacyclovir¹⁰⁹⁵ 1 G twice daily significantly improved scores on the Positive and Negative Syndrome Scale in outpatients with persistent schizophrenia and who were seropositive for cytomegalovirus (21 or 32.3% of the sample were seropositive for cytomegalovirus – interestingly, the drug didn't affect scores in herpes simplex type 1-seropositive patients[see Dickerson ea, 2003a above] or in patients seropositive for herpes simplex type 2¹⁰⁹⁶, Epstein-Barr, varicella-zoster, or human herpes virus 6)

Fatemi ea (1999): infection of mice with human influenza virus on day nine of pregnancy leads to thinner neocortex and hippocampus and reduced cortical reelin¹⁰⁹⁷ immunoreactivity in offspring

Brown ea (2005): high, but not moderate, maternal Toxoplasma IgG antibody titres associated with risk for schizophrenia spectrum disorders in offspring in US study

Babulas ea (2006): used obstetric records and found significantly increased risk of schizophrenia and other schizophrenia spectrum disorders in offspring of mothers who had genital infections periconceptually

¹⁰⁹⁴ For a review see Brown and Derkits.(2010)

¹⁰⁹⁵ Valacyclovir is rapidly converted to acyclovir after ingestion.

¹⁰⁹⁶ Brown ea (2006) found no support for a relationship between prenatal herpes simplex virus 2 type exposure and risk of schizophrenia.

¹⁰⁹⁷ Reelin: extracellular matrix glycoprotein secreted by GABA interneurons during development and in adults; probably involved in synaptic plasticity/morphological changes involved in learning.

Dalman ea (2008): follow up of Swedes found a *slight* increase in non-affective psychosis and schizophrenia in those with a history of CNS viral (but not bacterial) infection during childhood (especially mumps or cytomegalovirus)

Brown (2008) reviewed the literature on infection and schizophrenia and pointed out the difficulty of timing infection (e.g. T gondii¹⁰⁹⁸), the likely interaction of susceptibility (genes, development) and microorganisms, and the need for more rigorous research design (e.g. increasing statistical power)

Sørensen ea (2008): looked for maternal infections in Denmark; used broad and narrow definitions of schizophrenia; first trimester exposure was associated with increased risk for broad and narrow schizophrenia whereas second trimester exposure was associated with increased risk for schizophrenia but only in unadjusted analyses; the findings were especially strong for narrow (ICD-8) schizophrenia with earlier onset; post-hoc analysis found that upper respiratory infection and infection with gonococci were associated increased risk for schizophrenia; and the authors surmised that the effects of infection are mediated by transplacental passage of maternal cytokines in response to bacterial infection

Brown ea (2009): adult schizophrenia exposed (serologically documented) in utero to influenza and toxoplasmosis had impaired performance on WCST and Trail Making Test part B (Trails B) compared to those not so exposed

Hospital treated pyelonephritis in Finland may add to the effects of genes in increasing risk for schizophrenia in offspring (Clarke ea, 2009)

If viruses cause schizophrenic illnesses they probably only account for a minority of cases. (O'Shea, 1997; Westergaard ea, 1999) Also, influenza exposure¹⁰⁹⁹ in utero has been linked to later affective disorder in the Finnish population. (Machon ea, 1997)

Krause ea (2010) measured antibody titres to CMV, herpes simplex virus, Epstein-Barr virus, mycoplasma, Chlamydia, and toxoplasmosis in 31 patients with schizophrenia and 30 healthy matched control subjects.

There was a significant increase in positive antibody titres in patients with schizophrenia only for Chlamydia trachomatis ($p = 0.005$) and a trend to significance for Herpes simplex virus ($p = 0.055$).

Combining the different agents, patients with schizophrenia had a significantly higher rate of positive titres to infectious agents as compared to controls ($p = 0.04$). The authors suggest that schizophrenia is not caused by a specific infectious agent but is due rather to an immune reaction in the CNS.

There appears to be a shift from Type I (cellular) to Type II (humoral) immune response in schizophrenia.

Evidence for impaired Type I response comes from a small study (Freudenreich ea, 2010) where IFN- γ and TNF- α expression was relatively reduced in schizophrenia.

Secondary schizophrenia-like disorders

Some conditions that may be associated with a schizophrenia-like illness¹¹⁰⁰

Paralysis agitans¹¹⁰¹

Encephalitis lethargica and other forms of encephalitis

Cerebral syphilis

Sydenham's chorea

Temporal lobe epilepsy¹¹⁰²

Brain injury

Brain tumour¹¹⁰³

Wilson's disease¹¹⁰⁴

¹⁰⁹⁸ Niebuhr ea (2008) found a significant positive association between T gondii IgG antibody schizophrenia in discharged US military personnel.

¹⁰⁹⁹ 1957 epidemic.

¹¹⁰⁰ An ICD-10 disorder, not to be confused with DSM-IV schizophreniform disorder; syn. symptomatic schizophrenia. The symptoms of 'schizophrenia' in cases with organic brain disease are often of a paranoid-hallucinatory type, with retention of rapport and warmth, and a more benign course than that associated with 'true' schizophrenia. (McKenna, 2007, p. 383)

¹¹⁰¹ Some authors found a lower than expected incidence in Parkinson's disease.

¹¹⁰² 15% after 15 years of TLE.

¹¹⁰³ Cerebral gliomas, pituitary adenomas.

¹¹⁰⁴ Rare autosomal recessive (ATP7B gene on chromosome 13) disorder of copper metabolism. (Ala ea, 2007) McKenna (2007, p. 383) concluded that the frequency of something resembling schizophrenia in Wilson's disease was likely to be low.

Huntington's disease
 Narcolepsy¹¹⁰⁵
 Cerebrovascular disease
 Frontotemporal dementia¹¹⁰⁶
 Familial idiopathic basal ganglia calcification¹¹⁰⁷
 Demyelinating disorders¹¹⁰⁸

Some drugs that can precipitate paranoid-hallucinatory psychoses

Anticholinergics
 Bromocriptine
 L-dopa
 Psychostimulants like amphetamine
 Hallucinogens like LSD and PCP
 ACTH and steroids
 Disulfiram¹¹⁰⁹
 Indomethacin
 Digoxin
 Anti-malarials
 Anti-tuberculosis drugs
 Vigabatrin¹¹¹⁰

The hypotheses of a shared genetic basis between some cases of schizophrenia and coeliac disease and an abnormal intestinal permeability in some schizophrenics that might allow the passage of exorphins leading to behavioural problems is intriguing. (Dohan, 1966; Eaton ea, 2004) Does gluten precipitate schizophrenia in a minority of cases? One female with schizotypy known to the author has harassed many physicians, despite negative testing, in an effort to prove that her schizophrenic son has coeliac disease. A genetic marker (6p23-p22.3) in coeliac disease is very close to the dysbindin locus, which has been implicated in schizophrenia. (Straub ea, 1995)

Clinical features

'If one cannot hold information online or select what is relevant for task performance, then serious disruption in mental processes is likely to ensue.' (Banich, 2002)

(a) Premorbid findings

[1] This work is still at too early a stage to allow accurate prediction in individual cases.¹¹¹¹ Substance abuse is a confounder in such research and needs to be controlled for. A 1946 British birth cohort was followed up. Sitting, standing, walking and talking were delayed at 2 years. (Wadsworth, 1991) Foerster ea (1991) found that schizophrenic males had greater premorbid impairment than schizophrenic women or men with mood disorder. Poor premorbid adjustment predicted early age at first admission. Videos of schizophrenic patients taken during childhood have been interpreted as showing an excess of negative affect (Walker ea, 1993) or differences on measures of sociability and general neuromotor function from controls. (Schiffman ea, 2004) Perrin ea (2007) looked prospectively at a birth cohort of individuals with

¹¹⁰⁵ Must outrule effects of amphetamines. (Hyde & Lewis, 2003, p. 190) Amphetamine-induced psychosis in narcoleptics may require a change to modafinil.

¹¹⁰⁶ See Velakoulis ea (2009) and Schoder ea (2010). The two conditions share some symptoms (e.g. emotional blunting) but differ for others (e.g. delusions are rare in frontotemporal dementia). The risk for schizophrenia is increased in the close relatives of patients with frontotemporal dementia.

¹¹⁰⁷ Fahr's disease: an autosomal dominant condition.

¹¹⁰⁸ Is schizophrenia a disorder of myelin and oligodendroglia? (Davis ea, 2003) Microarray studies report downregulation of genes related to oligodendrocyte function and myelination in schizophrenic brain. (Peirce ea, 2006)

¹¹⁰⁹ Inhibits dopamine-beta-hydroxylase, increasing DA availability: may exacerbate schizophrenia, especially at > 250 mg/day.

¹¹¹⁰ Sabril, a GABA transaminase inhibitor.

¹¹¹¹ See *Dialogues in Clinical Neuroscience* 2005;7(1). The complete issue is dedicated to the early stages of schizophrenia.

and without schizophrenia spectrum disorder and found slower early, but not late, growth in females but not males who developed the disorder. In a study using both twins and siblings, Picchioni *et al.* (2010) found that schizophrenia was significantly associated with deficits in social adjustment and personality during childhood and adolescence and additive genetic effects best explained these phenotypic correlations. Johnstone *et al.* (2005) examined high risk young adults with a strong family history of schizophrenia and found that those who later developed schizophrenia were socially anxious, withdrawn, and had other schizotypal features. Jones *et al.* (1994) prospectively studied over 5,000 people born in one week in 1946. Thirty cases of schizophrenia arose between ages 16 to 43 years, giving a cumulative risk of 0.63%. The latter reached milestones, especially walking, later, had more speech problems, low educational test scores¹¹¹², solitary play preferences, less social confidence, and more social anxiety. Health visitors rated their mothers as having below average mothering skills and understanding of their children. Reports of less syntactically complex speech in premorbid children are contradictory, positive reports perhaps detecting state characteristics. In a 45-year follow-up study in Denmark (Sørensen *et al.*, 2010) people who developed psychiatric diagnoses other than schizophrenia reached most developmental milestones earlier than did those with a diagnosis of schizophrenia but later than did controls (people who were never admitted to a psychiatric department) and the two patient groups differed significantly for the age at which they could walk unsupported. Kremen *et al.* (1998), in their follow-up study, found that a decline in IQ during childhood was associated with later schizophrenia. This finding is supported by a Finnish report of a failure to progress in education despite early academic normalcy. (Cannon *et al.*, 1999) Morgan *et al.* (2008) point out that intellectual disability and schizophrenia often co-occur. A study of draftees in Israel (Davidson *et al.*, 1999) found that adolescents who later received a diagnosis of schizophrenia had poor social and intellectual functioning, as well as low organisational ability. Despite IQ scores within the normal range, apparently healthy Israeli adolescents who later manifest schizophrenia have intellectual decline. (Reichenberg *et al.*, 2005) Gunnell *et al.* (2002) in a cohort study of Swedish male conscripts, found that poor intellectual performance at age 18 years was associated with an increased risk of developing schizophrenia and other non-affective psychoses in early adult life. They attributed this phenomenon to the prodromal effects of psychotic illness rather than to problems encountered in utero or around the time of birth. It is likely that young people at high genetic risk for schizophrenia perform poorly on all tests of intellectual function and memory. (Byrne *et al.*, 1999) Hollis (2003a, p. 35) states that premorbid IQ appears to be lower in child and adolescent onset schizophrenia relative to adult onset cases and that this results from a downward shift of the whole distribution of IQ. Woodberry *et al.* (2008) found, in a meta-analytic review of 18 studies, that the mean IQ of people who developed frank psychosis years later was a one-half of a standard deviation below healthy controls and that IQ fell significantly when they fell ill. Cannon *et al.* (2001) found that suspiciousness, sensitivity, and peer relationship problems among attendees at a child psychiatric department to be predictive of schizophrenia in adulthood. A follow-up of the 1966 birth cohort from Northern Finland to age 34 (Isohanni *et al.*, 2006) found that impaired performance (e.g. delayed motor/intellectual development) or adverse exposures (such as pregnancy/birth complications, diseases of CNS) increased risk for schizophrenia; and, at least in the early phase, less flexibility and poor coping may precede schizophrenia.

Zammit *et al.* (2004) in a 27-year follow up, found that lower IQ was associated with increased risk for schizophrenia, severe depression, and other non-affective psychoses, but not bipolar disorder. Joyce *et al.* (2005) looked at community patients with first episode schizophrenia and found that half had preserved IQ in the normal range but with impaired spatial working memory; 40% had generalised cognitive decline; and low premorbid IQ was associated with earlier illness onset.

Combining high-risk status with cognitive disturbance may prove useful in predicting transition to psychosis. (Ruhrmann *et al.*, 2010)

Low pre-morbid IQ may predispose people to psychiatric patienthood across a range of diagnoses. (Urfer-Parnas *et al.*, 2010)

An Australian follow-up study found that young adults who screened positive for 'non-affective psychosis' (Welham *et al.*, 2009) or 'delusional-like experiences' (Scott *et al.*, 2009) demonstrated psychopathology during

¹¹¹² Poor school performance in all domains at age 16 was strongly associated with risk for schizophrenia and other psychoses in a Swedish national cohort study. (MacCabe *et al.*, 2008)

childhood and adolescence and that the psychopathological trajectory of children destined to develop schizophrenia anticipated the heterogeneous nature of the full disorder.

The *Bonn Scale for the Assessment of Basic Symptoms* has been used to detect prodromal schizophrenia. Absence of BSABS prodromal symptoms excluded the development of a first psychotic episode, with a probability of 96%, with the percentage of false negatives being only 1.3%.

[2] In cases of *childhood-onset schizophrenia*¹¹¹³, failure of predisposed children to progress normally may occur instead of regression, there may be markedly uneven development and an insidious onset of symptoms, there may be a delay in language¹¹¹⁴ and social development¹¹¹⁵, and visual hallucinations are more common than in adult cases. A decline in full-scale IQ during adolescence has been recorded in such cases that may reflect an inability to acquire new information and abilities rather than a dementia *per se*. The child can be requested to describe TV shows or movies in order to test their organisation and synthesis of information. In one study (Werry *et al*, 1991) only 61% of childhood onset cases of schizophrenia retained this diagnosis on follow up, the others being rediagnosed as bipolar disorder, schizoaffective disorder, or other psychoses. Insidious onset, poor premorbid functioning, and absence of prominent affective symptoms were found to predict diagnostic continuity as schizophrenia. Positive symptoms failed to tell schizophrenic from affective cases. Hollis (2000) found that a diagnosis of DSM-III-R schizophrenia in childhood and adolescence had good predictive validity, suggesting aetiological continuity with adult cases, but with a worse course and outcome. Hollis (2003b) reported that premorbid social impairment was more common in early-onset schizophrenia than in other early-onset psychoses; overall, impaired premorbid development, enuresis and incontinence during psychosis were specifically associated with the negative psychotic symptom dimension. Childhood-onset schizophrenia is associated with the same eye-tracking dysfunction as that reported in adult schizophrenia. (Kumra *et al*, 2001) The parents of such cases have a significantly higher morbid risk for schizophrenia spectrum disorders (24.74%) relative to parents of adult-onset cases (11.35%) and parents of community comparison subjects (1.55%). (Nicolson *et al*, 2003) Adolescent schizophrenics with childhood-onset schizophrenia may have excess loss of cortical grey matter in frontal, parietal, and temporal regions. (Rapoport *et al*, 1999; Gogtay *et al*, 2004) The rate of reduction in cerebral grey matter is related to premorbid impairment and baseline symptom severity. (Sporn *et al*, 2003) One MRI study has demonstrated lateral ventricular enlargement, smaller mid-sagittal thalamic areas, but no reduction in the volume of temporal lobe structures. However, a controlled MRI study of adolescent-onset schizophrenia reported reduced total and gray matter volumes in the right superior temporal gyrus. Collinson *et al* (2003), using MRI in 'early-onset' schizophrenics and normal controls, found smaller brains in the former group, especially affecting the left hemisphere in males; female and male cases had reduced rightward and leftward asymmetry relative to same-sex controls; and decreased left hemisphere volume in males and decreased rightward asymmetry in females correlated with reduced IQ. Owever, Bakalar *et al* (2009) followed up 49 right-handed childhood onset cases of schizophrenia (mean baseline age 14.72 years +/- 2.63) with MRI and compared them matched, healthy controls: no significant asymmetry differences were found.

MRS has shown increased ventricular size¹¹¹⁶, and midcallosal, posterior cingulate, caudate and thalamic abnormalities.

¹¹¹³ *Dementia precocissima*: prepubertal schizophrenia. Childhood-onset schizophrenia affects < one in 10,000 children. Less than one in a hundred people with schizophrenia had this diagnosis as children. Commoner causes of psychosis in childhood are major depressive disorder, bipolar affective disorder, and severe cases of dissociation, as may be found in posttraumatic stress disorder. (Khurana *et al*, 2007)

¹¹¹⁴ Including verbal memory.

¹¹¹⁵ Poor attention and motor skills.

¹¹¹⁶ Especially posterior horns of lateral ventricles.

(b) Schizotypal disorder (F21 in ICD-10)¹¹¹⁷

These people are eccentric, aloof, and have thinking reminiscent of schizophrenia¹¹¹⁸, but nothing definite and characteristic of schizophrenia has been manifested. There may be suspiciousness, paranoid thinking, unresisted obsessiveness, illusions (including somatosensory), depersonalisation/derealisation, and occasional transient quasi-psychotic episodes¹¹¹⁹ with little or no external provocation. Working memory is impaired. (Mitropoulou et al, 2005; Nienow & Docherty, 2005) The course, while fluctuating in intensity, is chronic. It only sometimes evolves into schizophrenia. (Kendler et al, 1991) A family history of schizophrenia is not uncommon. Nevertheless it is often viewed as part of a 'schizophrenic spectrum', along with (very variably) schizophrenia, schizoaffective disorder, paranoid personality disorder (Hans et al, 2004), other non-affective psychoses, and psychotic affective illness. It resembles a personality disorder, and is designated as such in DSM-IV. Features of this disorder can be found in relatives of patients with disorders other than schizophrenia or schizotypal (personality) disorder, especially in association with affective disorder, although schizotypal symptoms appear to be particularly common in the relatives of schizophrenic patients. (Kendler et al, 1995)

In a Northern Finnish birth cohort study (Lahti et al, 2009), schizotypal traits in adulthood (age 31 years) lower placental weight, lower birth weight and smaller head circumference at one year predicted increased positive schizotypal traits in females, and higher gestational age, poorer childhood family circumstances, an undesired pregnancy, birth in winter or autumn, higher birth order and a mother who smoked whilst pregnant predicted some schizotypal traits in both sexes.

Neuroimaging studies using schizotypal patients suffer from various methodological shortcomings (e.g. small sample size and a bias toward using male subjects) and therefore have to be interpreted with caution. (Parnas et al, 2005, p. 35) However, there is evidence for bilaterally reduced neocortical grey matter volume and larger sulcal CSF volume in schizotypal personality disorder in both sexes. (see Koo et al, 2006) A smaller left Heschl's gyrus¹¹²⁰ gray matter volume has been reported from Boston on MRI in schizotypal patients than in controls. (Dickey et al, 2002) Takahashi et al (2009b) found MRI evidence suggesting that a reduction in gray matter in the superior temporal gyrus (including Heschl's gyrus) may be specific to schizophrenia in an MRI study of patients with a first episode of one of a number of types of psychosis. The sexes should be studied separately because an MRI study of community-based females comparing schizotypal personality disorder and comparison subjects by the same authors found no superior temporal gyrus volume differences. (Dickey et al, 2003) People with schizotypal disorder show a relatively decreased activation of key frontal regions on fMRI while performing a visuospatial working memory task. (Koenigsberg et al, 2005)

Schizoid personality disorder does not appear to be as closely related to schizophrenia as was once thought. (Fulton & Winokur, 1993)

(c) 'Acute'

About one year passes on average between onset of psychotic symptoms and getting into treatment. The onset is often insidious¹¹²¹, the person becoming more withdrawn and introverted, avoiding friends, losing drive, dropping out of activities, and developing an interest in subjects like psychoanalysis, occultism or

¹¹¹⁷ Once labelled as having 'latent' or 'borderline' schizophrenia (as were schizoid personalities).

A related concept is that of *schizotaxia*, (Meehl, 1962) an old idea that has been modified over the years. Genetically vulnerable individuals are exposed to early adversity, such as birth anoxia, leading to abnormal development of certain brain structures. In childhood, the presentation of this liability to schizophrenia presents as 'schizotaxia' as shown by various degrees of cognitive, neurobiological and social deficits. It has been suggested that 20-50% of first-degree relatives of schizophrenics are schizotaxic. Most cases remain schizotaxic but some will develop schizotypal disorder or schizophrenia. There is some evidence for improved function in people with schizotaxia who are given low-dose risperidone. (Tsuang et al, 2002)

This is an old concept that has been modified over the years. Genetically vulnerable individuals are exposed to early adversity, such as birth anoxia, leading to abnormal development of certain brain structures. In childhood, the presentation of this liability to schizophrenia presents as 'schizotaxia' as shown by various degrees of cognitive, neurobiological and social deficits. 'Delusional proneness' (e.g. feeling conspired against, telepathic thinking, or hearing voices) may be more common in first-degree relatives of schizophrenics or bipolars. (Schürhoff et al, 2003)

¹¹¹⁸ Magical, cold, odd, peculiar, circumstantial, metaphorical, overelaborative, stereotyped, no gross incoherence.

¹¹¹⁹ Intense illusions, hallucinations, and delusion-like ideas.

¹¹²⁰ Like the planum temporale, **Heschl's gyrus** is a component of the superior temporal gyrus. Heschl's gyrus and other superior temporal areas (including primary and secondary auditory cortices) may be involved in auditory hallucinations in schizophrenia. (Nenadic et al, 2010)

¹¹²¹ Perhaps this is so in a majority of cases.

astrology. Delusions¹¹²² and hallucinations eventually appear. Some cases come on more abruptly, perhaps following a stressful event; they are floridly ill, feel that they are the object of special attention, attach abnormal significance to the mundane, have bizarre (completely implausible) ideas, may be mute, and may have first rank symptoms (FRS). Any sensory modality may be affected by hallucinations, but most commonly these are auditory. Auditory hallucinations may be in any person, speaking to or about the patient. Their content is very variable and is not always clear to the sufferer. They tend to be persistent. The time-honoured differentiation between true and pseudo-hallucinations can be very difficult to make in practice. Affect is usually abnormal. There may be perplexity (ideas of reference, persecution or grandiosity may be fleeting), depression or elation¹¹²³, flattening or blunting of affect, anger, or incongruous emotional display (e.g. fatuous giggling when sadness would be more appropriate). Behaviour may be characterised by withdrawal, bizarre activity, or catatonia (*vide infra*). Full-blown catatonia is more likely to be seen today in people coming from the Third World or in people from isolated localities. However, catatonia has many causes other than schizophrenia and more subtle manifestations should be actively sought. (Fink & Taylor, 2009) Deaf schizophrenic patients may show evidence of thought disorder in their sign language¹¹²⁴.

(d) ‘Chronic’

Positive symptoms such as hallucinations and delusions become less dominant. There may be a ‘defect state’ with lack of vivacity and enthusiasm, emotional unresponsiveness, apathy, poverty of speech, inability to form more than fleeting interpersonal ties, anhedonia, loss of employment or marriage, and impaired effectiveness in social roles, including parental responsibilities. Most cases will have recurrent episodes with positive symptoms, often without any prodrome. Many will develop depression.

(e) Thought disorder¹¹²⁵

Not all cases demonstrate this. It is not confined to schizophrenia, being found, e.g. in mania. Abstract thinking is more a function of low intelligence than thought disorder. The interviewer finds it difficult to get straightforward answers to simple questions. Answers are vague and irrelevant. There is a tendency to slip off the theme when talking. There is poor continuity between sentences. Unlike the dysphasic, the schizophrenic has no idea that he is difficult to understand. He is preoccupied with abstruse ideas. Quantity of speech declines and there is deterioration in sentence construction. Less words than normal are employed, words, phrases and even syllables are repeated. Constructs are unstable and idiosyncratic. An excess of thought disorder has been found in relatives of schizophrenics and interpreted as being due to shared genes rather than rearing. (Kinney ea, 1997) Using a test of *sensorimotor gating* called *prepulse inhibition*¹¹²⁶, Perry ea (1999) found a close association between gating difficulties and thought disturbance – trivia cannot be filtered out from conscious awareness. Others have found profound deficits of prepulse inhibition of the acoustic startle response in early- but not late-onset schizophrenia, while others found evidence for defective prepulse inhibition, probably genetically transmitted, in schizophrenia spectrum disorders, including schizotypal personality disorder (Hazlett ea, 2003) and the relatives of patients with schizophrenia. A reduction in prepulse inhibition is found in a number of disorders, e.g. OCD, Huntington’s disease, and Tourette syndrome. (Ellenbroek & Cools, 2002) Prepulse inhibition levels are influenced by sex (higher in males), people on atypical antipsychotics, and smoking status (higher in smokers). (Swerdlow ea, 2006) Prepulse inhibition may be regulated by dopamine neurotransmission in the prefrontal cortex and its levels seem to depend on the COMT Val158Met gene polymorphism. (Roussos ea, 2008)

(f) Early onset schizophrenia

Alaghband ea (1997) examined children and adolescents with onset of schizophrenia before age 12 years. Males more often had an insidious onset. Smaller cerebral volumes on MRI were associated with negative symptoms. The authors felt that their findings supported continuity between early and later-onset cases.

¹¹²² Patients with schizophrenia tend to justify abnormal beliefs in an illogical fashion.

¹¹²³ **Elation** can occur in a number of psychiatric disorders, e.g. acute schizophrenia, mania, and drug-induced states.

¹¹²⁴ Interestingly, in a small study, Mason ea (2008) found an odds ratio of recorded middle-ear (especially left-sided) disease pre-dating schizophrenia of 3.68 – auditory hallucinations were associated with middle-ear disease but not with deafness. The idea that ear disease causes insanity by brain irritation is old. (Bryant, 1906)

¹¹²⁵ Some authorities prefer ‘speech disorder’.

¹¹²⁶ Reduced P50 suppression and prepulse inhibition do not necessarily occur together. (Hong ea, 2007)

Kendler et al (1994) found no evidence from a familial perspective to support an aetiological distinction between the modern subtypes of schizophrenia. The ICD-10 description of schizophrenia is outlined in the box. DSM-IV is also discussed in the same box. DSM requires 6 months for the diagnosis, ICD only one month. The former insists on deterioration in functioning whereas the latter does not. Each symptom is present in some patients, but none is found in all. DSM-IV schizophrenia is basically a diagnosis by exclusion; individual symptoms are not confined to schizophrenia, being found in conditions such as affective disorders and dementia; the condition is over-simplified and reduced to the smallest common denominator; and it is more suitable for an experienced psychiatrist doing research than for the newcomer. (Maj, 1998)

Schizophrenia

(a) ICD-10, F20

There are fundamental distortions of thinking and perception, and inappropriate or blunted affect. Onset can be acute with disturbed behaviour, or insidious with gradual development of odd ideas and conduct. Course is variable and specifiable (by 5-character categories) as continuous, episodic with progressive/stable defect, episodic remittent, incomplete/complete remission, other, and observation less than a year. In some cases, there may be complete or virtual recovery. It affects the sexes equally, onset being later in females. There are no strictly pathognomonic (read: diagnostic) features. *Symptoms must be present for at least one month* (except for simple schizophrenia where at least one year is required). Otherwise, diagnose *acute schizophrenia-like disorder* (F23.2) until and if a month elapses with symptoms. The one-month criterion only applies to certain symptoms: thought echo, delusions of control, commenting hallucinatory voices, culturally inappropriate and completely impossible persistent delusions, persistent hallucinations in any modality, breaks/interpolations in train of thought, catatonic behaviour, and negative symptoms such as blunt affect or self-absorption. It does not include a retrospective recognition of a prodrome: loss of interest, social withdrawal, poor hygiene, anxiety, mild depression, preoccupation, etc. (Relatives and friends may minimise or rationalise prodromal symptoms.) Schizophrenic symptoms must antedate affective ones during the first month of the illness proper; if they commence simultaneously and are evenly balanced the diagnosis is schizoaffective disorder (F.25). Avoid a diagnosis of schizophrenia in the presence of overt brain disease or during drug intoxication/withdrawal. Similar conditions developing in the presence of epilepsy or other brain disease are coded under F06.2, and those induced by drugs under F1x.5.

Subtypes:

- F20.0, paranoid¹¹²⁷ (includes paraphrenic schizophrenia) – relatively stable, often paranoid, deluded, usually hallucinated – especially auditory, perceptually disturbed; disturbances of affect, volition, and speech, and catatonic symptoms are not prominent; onset usually relatively late.
- F20.1, hebephrenic (includes hebephrenia and disorganised schizophrenia) – usually starts 15-25 years of age; poor prognosis; prominent affective changes; fragmentary delusions/hallucinations; irresponsible, unpredictable behaviour; mannerisms are common; grimacing; pranks; mood shallow and inappropriate, with giggling or self-satisfied, self-absorbed smiling, or a lofty manner; hypochondriacal; reiterated phrases; disorganised thinking; rambling/incoherent speech; loss of drive.
- F20.2, catatonic – nowadays uncommon in the West; prominent psychomotor disturbances; can alternate between hyperkinesis and stupor, or automatic obedience and negativism; constrained attitudes and postures held for long periods; may show violent excitement; may have oneiroid state (Q.V.) with vivid scenic hallucinations; perseveration of words/phrases; transient and single symptoms can occur in other subtypes of schizophrenia; catatonic symptoms not diagnostic of schizophrenia, as will be discussed later.
- F20.3-9, undifferentiated (can't be subtyped), post-schizophrenic depression (some, non-dominating schizophrenic symptoms still present), residual (chronic negative symptoms; more or less synonymous with 'chronic schizophrenia'), simple (uncommon, insidious, odd, socially incompetent, declining

¹¹²⁷ Some say this is the commonest type but others would say that undifferentiated schizophrenia is the most common.

performance, progressive, no positive symptoms at any stage, aimless, idle, self-absorbed, may be vagrant), 'other', and 'unspecified'.

(b) DSM-IV

'Schizophrenia and other psychotic disorders' include disorders that have psychotic symptoms as their defining feature. According to DSM-IV, other conditions, such as Alzheimer's disease, psychotic mood disorders, and substance-induced delirium, do have psychotic symptoms but not as their defining feature.

- *Schizophrenia*. The disturbance has lasted at least 6 months, including at least 1 month of active-phase symptoms: 2 or more delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, negative symptoms. The subtypes are: paranoid¹¹²⁸ (preoccupation with 1 or more delusions or frequent auditory hallucinations), disorganised¹¹²⁹ (disorganised speech and behaviour, flat or inappropriate affect), catatonic (motor immobility, excess motor activity, extreme negativism, peculiarities of voluntary movement, echolalia, echopraxia), undifferentiated (not meeting criteria for foregoing subtypes – commonest type in clinical practice), and residual (no prominent symptoms or signs, but has attenuated features, e.g. odd beliefs, unusual perceptual experiences). Detailed guidelines are given for describing the course of chronic illness.
- *Schizophreniform disorder*. Similar to above but lasting 1 to 6 months. The term schizophreniform psychosis was used in DSM-III-R to prevent the premature diagnosis of schizophrenia, although first episode schizophreniform cases may be as cognitively dysfunctional as are cases of chronic schizophrenia. (Heff ea, 1992) Schizophreniform disorder is heterogenous, some cases developing schizophrenia, schizoaffective disorder, a mood disorder, or other psychiatric disorder. (Ho ea, 2003, p. 397) Some cases are acute and brief with a relatively good outcome. (Marneros & Pillman, 2007, p. 100)
- *Schizoaffective disorder*. A mood episode plus active phase schizophrenic symptoms occur together and are preceded or followed by at least 2 weeks of delusions or hallucinations without prominent mood symptoms.
- *Delusional disorder*. At least 1 month of non-bizarre delusions without other active phase schizophrenic symptoms. Seven subtypes, depending on the prominent delusional theme: erotomaniac, grandiose (megalomania, delusions of personal greatness), jealous (infidelity of sexual partner), persecutory (persecution of self or of others emotionally close to self), somatic (false belief one has physical defect or general medical condition; monosymptomatic hypochondriacal psychosis: parasitophobia, insects in skin, dysmorphophobia or body dysmorphic disorder, body odours¹¹³⁰, and non-functioning body parts), mixtures of foregoing, and unspecified because delusions do not fit into any specified category.
- *Brief psychotic disorder*. Psychosis lasting more than a day and less than a month.
- *Shared psychotic disorder*. Cf. folie à deux.
- *Psychotic disorder due to a general medical illness or induced by chemicals*. A period of observation may be required before attributing psychosis to a drug.

The existence of simple schizophrenia¹¹³¹ remains controversial. Kendler ea (1994) found simple schizophrenia to be rare, debilitating, similar to 'typical' schizophrenia in presentation and course except for the absence of positive symptoms, and, from a family perspective, it appeared to be related to 'typical' schizophrenia.

Males with schizophrenia appear to be more prone to suffer from a defect state than do schizophrenic women, although this is not an absolute.

¹¹²⁸ Do not diagnose paranoid subtype in the presence of disorganised speech or behaviour, flat or inappropriate affect, or catatonia.

¹¹²⁹ **Disorganised** is synonymous with **hebephrenic**: early onset, poor social/occupational functioning, more severe illness, and poorer longterm prognosis than the paranoid subtype. The patient may be deluded and hallucinated but these phenomena are not as prominent as in the paranoid subtype. Do not use this diagnosis if criteria for catatonic subtype are met.

¹¹³⁰ More often seen by dermatologists and may respond to antipsychotics, including pimozide.

¹¹³¹ '**Simple schizophrenia**', simple deteriorative disorder in DSM-IV, is attributed to Diem who described it in 1903. However, Clouston, Pick and Sommer and others described a similar state before him).

An interesting phenomenon found in chronic schizophrenics is temporal disorientation¹¹³². Elvevåg ea (2003) found that schizophrenics are relatively inaccurate at estimating brief time periods (< 1 s). Thought disorder might be due to dysfunction of the cortico-subcortical loops that project into the prefrontal cortex.

Medication can impair attention. Therefore drug-naïve patients are ideal subjects for neuropsychological testing.

Executive processes include a broad range of operations involved in initiating and maintaining controlled information processing and co-ordinated mental activity. Included are goal or context representation and maintenance, attention allocation and stimulus-response mapping, and performance monitoring.¹¹³³

According to Goldberg ea (2003, p. 171), impaired executive function in schizophrenia is a core deficit that is independent of IQ. However, Dibben ea (2009), who found (in a meta-analysis) that negative symptoms and disorganisation are associated with partially dissociable patterns of executive impairment¹¹³⁴, believe that co-existing intellectual impairment (low IQ) has been a confounding factor in research. Also, studies of executive function should control for substance use. (Rodriguez-Jimenez ea, 2010) Barnett ea (2005) argue that impaired executive function (as tested by attention-shifting) is a stable, trait-like at onset of psychosis. The neural network involved in executive function includes the DLPFC and the anterior cingulate cortex. Besides disturbances in these areas, functional imaging studies in schizophrenia have reported disturbances in tempero-limbic regions, including the hippocampus, superior temporal gyrus, striatum and cerebellum. In a meta-analysis, Bora ea (2009) found no categorical differences in terms of cognitive functioning between schizophrenia, schizoaffective disorder and affective psychosis, except that a subgroup of schizophrenia sufferers with particularly severe negative symptoms may be more cognitively impaired than those in the other groups.

Gross cognitive impairment in schizophrenia was found by Buhrich ea (1988) to be related to the disease and not premorbid intellectual impairment or past physical treatment. However, according to Mesholam-Gately ea (2009), who conducted a meta-analysis of 47 studies of first episode schizophrenia, cognitive impairment is present by the time of the first episode and does not differ substantially from established illness, and IQ is lower at first episode than in the premorbid state and remains stable thereafter. Stahl (2003) suggests that antipsychotic drugs may improve working memory by releasing DA and NA in the dorsolateral prefrontal cortex (DLPFC). Hyde ea (1994) found that intellectual function did not decline markedly during the course of schizophrenia, suggesting to the authors that schizophrenia was more likely to be a static encephalopathy than a dementing disorder. Most schizophrenic patients perform poorly on IQ tests. Such deficits have been found to predate onset of disorder and to be lifelong. (Russell ea, 1997) Both general intellectual impairment and thought disorder are naturally associated with poor performance on language tests. Walder ea (2006) found that language was more impaired in males than in females with schizophrenia, but that phonology was, relative to controls, more affected in the female patients. Verbal memory (see Leeson ea, 2009) is defective from the beginning of a schizophrenic illness, and the extent of this deficiency may be greater the earlier the age at onset of the illness. (Tuulio-Henriksson ea, 2004) Episodic memory dysfunction, which may be due to reduced parahippocampal connectivity, (Talamini ea, 2005) may point toward a poor outlook. In fact, schizophrenics may even confabulate¹¹³⁵ with answers that

¹¹³² Classically out by about five years in their determination of how long they are in hospital. Patients have difficulty in giving their ages correctly (*age disorientation* – usually the patient says they are much younger than their chronological age) or telling the time. These are probably not delusions and probably reflect cognitive difficulties.

¹¹³³ Put simply, the generation and implementing of plans depend on intact executive processing. Schizophrenic patients have difficulty solving a problem when the solution is not obvious or when they must use the knowledge they already possess in a novel way. They find it difficult to keep information ‘in the forefront of their minds’ (on-line). When testing different races for cognitive function it is essential to control for confounding variables such as education and motivation. (Joyce & Huddy, 2004) Findings in first-episode schizophrenia include poor ability to plan, poor ability to recall a story and learn unrelated word pairs, but intact ability to shift attention from one set to another; and inability to predict the wishes and intentions of others (deficits in ‘theory of mind’), made worse by a low premorbid IQ.

¹¹³⁴ E.g. clinically stable patients showed significantly higher correlations with executive impairment than did those with unstable illness, and negative symptoms as well as disorganisation were related to current IQ.

¹¹³⁵ So-called ‘*delusional confabulation*’ (‘*confabulatory paranoia*’) is manifested by the patient apparently making up fantastic delusional memories as needed. These ‘recollections’ are subject to change and elaboration during an interview. (McKenna, 2007, p.4) Mullen (2008, p. 27) writes that whilst the listener may be tempted to dismiss this phenomenon as malingering (because of the tendency of the patient to respond to suggestions or scepticism on the part of the listener) a prolonged encounter will convince the examiner that it is abnormal.

reveal a poor understanding of the gist or moral of a story they are asked to recall. (Lorente-Rovira et al., 2007) Cutting and Murphy (1988) found that 75% of schizophrenics were markedly deficient, relative to neurotic patients, in their knowledge of everyday social issues. Elderly schizophrenics have been reported to demonstrate greater cognitive deterioration than can be accounted for by necropsy evidence of a dementing process. (Purohit et al., 1998) Wood et al. (2002) found that recognition memory deficits were common to early and established schizophrenia, whereas impaired associative learning was confined to the established cases. According to González-Blanch et al. (2008) cognitive impairment is common in first-episode psychosis regardless of good prognostic features such as short illness duration, being female or having a later illness onset, and negative family history of psychosis. Researchers (Brewer et al., 2005; Barnett et al., 2005; Tiihonen et al., 2005) have reported visuospatial processing impairment and some memory deficits prior to full development of psychosis. Cannon et al. (2002) in their prospective New Zealand study from childhood to adulthood, found that later DSM-IV schizophreniform disorder (at age 26 years) was associated with significant impairments in neuro-motor, receptive language, and cognitive development in childhood, and that developmental impairments also predicted self-reported psychotic symptoms at age 11 years. Reichenberg et al. (2010) examined a cohort of males and females born 1972-3 in Dunedin, New Zealand, when they were aged 3-32 years: children who went on to develop schizophrenia in adults entered primary school with major problems of verbal reasoning and they lagged behind other children in working memory, attention, and processing speed as they aged. Schubert and McNeil (2005) looked prospectively at offspring (mean age 22.3 years) of mothers with a history of psychotic disorders and found (compared with normal risk offspring) significant impairment of verbal memory, selective attention, and grammatical reasoning. Such impairment identified more cases at risk for schizophrenia-spectrum psychosis than for affective-spectrum psychosis.

The left hemisphere is superior in its use of syntactic or semantic information, the right hemisphere being better for contextual information. It has been suggested that thought disorder relates to poor organisation of semantic memory. Schizophrenic patients are better able to recall concrete facts about social situations but seem impaired when attempting abstract deductions, e.g. they can remember the words used by an actor but are less able to describe his affect or goals. There may be no problem in recalling that an event happened, but there may be difficulty remembering when it occurred, a so-called context memory deficit. Not surprisingly, patients with schizophrenia may tend not to recall past achievements but rather recall hospitalisation and the stigmatisation of illness. (Raffard et al., 2009) Schizophrenic patients find it difficult to fill in deliberately deleted words from a narrative or to interpret a partial narrative. Elderly chronic schizophrenics may perform particularly poorly on tests of naming and constructional praxis. Both poverty of speech and incoherence of speech could be due to difficulties retrieving words from an internal lexicon, the former reflecting premature cessation of searching for words and the latter being related to incorrect word selection. The unaffected close relatives of schizophrenic patients have an excess of impaired information processing and deficits in working memory. Neuropsychological testing supports a relationship between temporal lobe dysfunction and reality distortion. (O'Shea, 1997)

Deficits in theory of mind ('mentalising ability' – ability to determine others' attitudes, beliefs and intentions) have been reported in children who later developed schizophrenia¹¹³⁶ (Schiffman et al., 2004) and in adult schizophrenics (e.g. difficulty in distinguishing between sarcasm and sincerity: Leitman et al., 2006; Horan et al., 2009), but results have not always been consistent. (Kern et al., 2009) Mizrahi et al. (2007) felt deficits may be less pronounced in schizophrenia, where they tend to be associated with negative symptoms, than in autism.¹¹³⁷ However, a meta-analysis (Sprong et al., 2007) found that all symptom subgroups (especially disorganised) and patients in remission had deficits in theory of mind. Patients with schizophrenia have problems integrating what they see (articulatory motions like lip movement and facial expression) with what they hear; an fMRI study (Szycik et al., 2009) that this problem stems from dysfunction of the speech motor system¹¹³⁸ in the right hemisphere and, possibly, reduced lateralisation of language functions to the

¹¹³⁶ Deficits in this area are also found in bipolar affective disorder of various ages and mood state. (e.g. Schenkel et al., 2008) There have been many reports (e.g. Lysaker et al., 2009) suggesting that individuals with schizophrenia have difficulty recognising the emotions of other people.

¹¹³⁷ Couture et al. (2010) used a battery of tests that examined social cognition and found that people with high-functioning autism resembled schizophrenia patients with negative symptoms more than schizophrenia patients with paranoid symptoms.

¹¹³⁸ Pars opercularis, middle frontal sulcus, and superior temporal gyrus.

left hemisphere. Bach et al (2009) suggest that people with schizophrenia have a general difficulty in identifying high-clarity emotional cues.

Other reports in schizophrenic patients are listed in the box.

Cognition and schizophrenia (roughly in order of time when published; scz = schizophrenia/schizophrenic; FES = first-episode scz; PFC = prefrontal cortex)

Difficulties on verbal short-term memory tasks due to limited 'representational capacity' and maintenance of information over delays

In elderly scz cognitive impairment predicted overall outcome and specific adaptive deficits, whereas positive symptom severity correlated more with specific adaptive deficits than with overall adaptive outcome

Significant cognitive decline in scz is not explained by age, whereas slow, gradual decline can be so explained

Impairment of mnemonic strategies despite preservation of IQ

Women with scz may be less vulnerable to certain cognitive deficits, especially those involving verbal processing, than are males with the disorder

Some cases have selective a deficit in verbal memory despite normal motivation, attention and general perceptual function, whereas others have multiple cognitive deficits

Greatest reduction in brain potentials associated with cognitive processing over the left temporal lobe

Problems in the attribution of desires and attentions to others as demonstrated using theory of mind comic strips

Scz unable to link separate aspects of events into a cohesive, memorable, and distinctive whole (*autonoetic* awareness - type of awareness involved in mentally reliving events from the personal past - is defective)

Scz patients have considerable cognitive dysfunction in the first 4 to 5 years of illness that remains stable at 1 to 2 standard deviations below that of comparison subjects, with little evidence of cognitive deterioration during that time except for verbal memory

Only negative symptoms associated with poor cognitive outcome

Performance and full scale IQ improved over first 5 years of illness, but verbal IQ remained stable

Abnormalities in eye movements, frontal release signs and short-term memory problems were associated with poor neuropsychological test results

Infant offspring of scz mothers may have impaired cognitive development (such results are confounded by birth weight and social status)

Healthy people have no difficulty with the Wechsler Digit Span Test (forward test measures general attention, backward test measures verbal working memory), relatives of patients have problems with the backward test, and patients have problems with both parts of the test suggesting a generalised verbal memory deficit

Scz usually have impaired explicit but preserved implicit function.

Most severely disabled scz have the most marked executive and attentional problems (despite stabilisation of psychosis)

Schizotypal personality disorder associated with impairment in working memory (but not perhaps in discrimination of form and trajectory)

Relatives of scz have poor attention as measured by Continuous Performance test (CPT) – MRI and CPT on drug-naïve FES suggests working memory deficit due to impairment in context processing due to deficits in DLPFC activation

Prompts and cues help scz patients to tackle chores sequentially

Cross-sectional study of elderly scz suggests scz have stable cognitive impairment

51% of scz patients showed cognitive decline; executive function and attention deficits may be core features of scz and independent of IQ variations

In a catchment-based study cognitive dysfunction was found to be pervasive in scz, the main affected area being memory

Duration of untreated symptoms does not explain widespread cognitive deficits, ventricular enlargement, and some loss of cortical mass in FES

Scz patients fail to form and use transient memory traces to guide behaviour (event-related potential study)

Poor outcome in scz associated with sensory processing dysfunction (tone-matching threshold study)

Neuropsychological impairment in ambulatory scz remains stable over time (did not include 'back ward' patients)

Tryptophan depletion in scz impaired executive function only, leaving, for example, mood uninfluenced

In test of object recognition, scz is associated with impaired perceptual closure that is improved to non-patient level with prior exposure to the objects (pictures) and the giving of valid word prompts; performance declines with increase in severity of negative symptoms

Study of sustained attention from Edinburgh (high-risk participants, controls, and FES) found that deficits were not associated with a genetic vulnerability to scz or with occurrence of psychiatric symptoms

Smaller anterior (but not posterior) hippocampal volumes on MRI in FES males (but not females) with poorer executive and motor function

Working memory tested by introducing a delay element: authors suggest that there is dysfunction in scz of posterior brain areas mediating visual perception processes and of prefrontal areas involved in active maintenance of information

In a controlled EEG/high-resolution event-related potential study, scz showed lower amplitude of mismatch negativity for across-phoneme changes than for change in duration of tone or vowel; for across phoneme change, scz had lower bilateral amplitude of mismatch negativity; scz also had significantly weaker L temporal combination of current sink (perpendicular sinking into scalp) and current source (arising out of scalp) and significantly weaker R frontal/temporal current sink than comparison subjects

Continuous Performance Test (measures sustained attention) is a stable vulnerability indicator for scz, is particularly abnormal in bipolar patients if psychotic, and is state-dependent in major depression

Patients with deficit scz had poorer adjustment in childhood/early adolescence and more impaired complex motor act sequencing (suggests fronto-parietal dysfunction) than non-deficit scz

Scz patients in remission performed worse on an irony task but not on other theory of mind tasks: interpreted as suggesting a trait deficit

Working memory components (perceptual competency and holding stimuli on-line – measured with a visual delayed match-to-sample task) all affected in FES, even if unmedicated

When people with scz try to think about beliefs/intentions of others they use analogical reasoning

Impaired working memory deficit in stable chronic male schizophrenics tested with neuropsychological test battery: appears to be a core component of the disorder

Chronic scz may have difficulty comprehending written material, although thought disorder (e.g. tangentiality) may play some role

Global intellectual impairment present at illness onset but does not decline over time (cross-sectional study favouring neurodevelopmental hypothesis)

N-back working memory task plus fMRI suggest that scz whose performance resembles healthy controls use greater prefrontal resources but achieve lower accuracy, and that other scz fail to sustain prefrontal network that processes the information and achieve even lower accuracy as a result

Chronic scz in encounters with mental health professionals recognised that others did not share their delusions and attempted to reconcile others' beliefs with their own; while recognising that they did not convince professionals they did not make their claims understandable; and the ensuing disagreement did not lead them to modify their beliefs: psychotic beliefs are not changed just because it is realised that they are not shared

First-episode unipolar psychotic depressives had similar (but less severe) neuropsychological dysfunction as did neuroleptic-naïve scz; non-psychotic unipolar depressives had mild attentional dysfunction

Marked deficits in ability of scz subjects in ability to interpret social cues from faces; those with positive symptoms were impaired in recognising even basic facial cues

Mismatch negativity deficits in scz is associated with poor everyday functioning

Schizophrenic patients have a specific deficit in context processing

Intellectual deficits relate to genetic liability to scz

Visual processing dysfunction exists early in scz and may be due to decreased non-linear signal amplification, consistent with glutamatergic theories; dysfunction occurs within low-level visual pathways involving thalamo-cortical radiations

Modafinil may enhance short-term memory in scz (inconsistent findings); it may elicit early gene expression in anterior hypothalamus and anterior cingulate cortex in animals; it increases activation in anterior cingulate cortex in humans (on fMRI) undertaking working memory task

Scz and schizophreniform subjects have a deficit in the initial process required to maintain information, e.g. ability to form an internal representation of complex objects

Presumed obligate carriers for psychosis (close relatives with psychosis) had impaired verbal memory and visuospatial manipulation

Mismatch negativity deficits and their relationship to poor functional status are stable over time in chronic scz

Poor ability to perceive and discriminate emotional expressions present at onset of scz and show minimal response to effective antipsychotic treatment

Emotion recognition deficits in scz are trait features that worsen with length of illness

Intellectual asymmetry with relative superiority of verbal skills to spatial skills represents a possible endophenotype of schizophrenia

Faulty inhibitory mechanisms for negative information may not be general in scz but may be selective for depressed cases

Origins of thought disorder may be closely linked to deficient executive functioning and semantic processing

Deficits in early stages of face perception in scz, and these deficits are associated with small fusiform gyrus volume

Decreased activation in whole thalamus, anterior nuclei, and medial dorsal nucleus in scz whilst performing memory tasks, e.g. N-back task for working memory

Scz is associated with a specific deficit of relational memory (ability to learn associations between individual items); this is associated with impaired function (fMRI) of parietal cortex and hippocampus

Psychotic (esp. positive symptoms) people use externalising bias when explaining negative social events, and this attribution style is not part of vulnerability to psychosis

Visuospatial dysfunction may be an association between brain-derived neurotrophic factor Met (BDNF_{Met}) variant and poor temporal lobe-related memory performance in scz

fMRI results suggest unstable cortical signal processing underlies classic abnormal cortical activation patterns as well as psychosis in scz

Working memory and executive cognition may be affected by abnormal hierarchical organisation of PFC in scz, the latter resulting in loss of functional specialisation and integration at dorsal PFC and compensatory activation from ventral PFC

33 year follow-up of scz; baseline impairment in verbal and non-verbal intelligence; significant decline over time in non-verbal intelligence only

Impaired attention/sequencing highly predict communication failures related to language structure in scz

Medicated chronic scz, especially with positive thought disorder, have inappropriate increases in activity in inferior prefrontal and temporal cortices in response to semantic associations on fMRI

Lorazepam impaired working memory and flumazenil enhanced working memory in chronic scz more than in healthy volunteers

Donepezil tried in 20 chronic scz with severe cognitive impairment: no improvement in cognition or negative symptoms

Neurocognitive measures are associated with scz, differentiate unaffected relatives from comparison subjects, and may have significant presumed heritability

Frontal release signs scores inversely correlate with IQ in scz

Scz and healthy siblings showed impaired emotion recognition but normal gender recognition – did not improve in scz despite clinical improvement (therefore phenotypic of scz)

Deficits in facial recognition may pre-date overt psychosis

Event-related brain potential study (N400 following sight of prime and target words of different relatedness levels) in scz suggests lack of direct and indirect semantic priming¹¹³⁹

Meta-analysis provided qualified support for semantic priming underlying schizophrenic thought disorder – but it might simply be a reflection of generalised slowed reactions

Meta-analysis showed improvement in most cognitive tasks in scz over time; practice may account for more improvement than did cognitive remediation; semantic verbal fluency is likely to be a cognitive endophenotype of scz

Patients with scz, and to a lesser extent their well siblings, are inclined to see trustworthiness in faces deemed untrustworthy by healthy controls

When testing facial emotional recognition the use of faces from races other than the patient's can lead to spurious results

Patients with scz have reduced ability to detect humour but have unimpaired appreciation of humour

Patients with scz who have hallucinations and delusions are more likely to misattribute source of negative (relative to neutral) words to others than to the self compared to scz in remission

Scz is associated with an increased tendency to accept as trustworthy (liberal acceptance) material that a non-scz would tag as untrustworthy

Neuropsychological impairment in scz resembles that seen with brain damage in terms of severity and stability; poor test results translate into real-life cognitive failures

Global measures employed may not be appropriate when attempting to find specific relationships between symptoms and executive functions; the interactions are complex

Women's superior ability (vs men) in identifying affective prosody and emotional content of the spoken message is better preserved in scz and the male advantage (vs women) in visuospatial processing is compromised in scz

Similar scores on several dimensions of neurocognitive function and psychopathology among DSM-IV scz and schizoaffective/bipolar affective disorder with psychotic features (versus community control group); relationship between neurocognitive function and psychopathology similar in both patient groups – suggests neurobiological continuum

151 cases of first-episode psychosis: lower performance on verbal and working memory associated with poor outcome at 6 months of treatment

Relative to controls, greater signal strength is needed for visual and cognitive processing of facial information in scz

Relative to controls, scz out-patients are impaired in their ability to recognise that they were the source of an earlier mental event

Cell membrane essential fatty acid composition and dynamics are associated with semantic memory and language in scz

Total eye scanning length and responsive search score, being parameters of exploratory eye movement, discriminate schizophrenia (sensitivity 73.3%, specificity 79.2%) from patients with mood disorders or neurotic disorders and from normal controls

First-episode scz is associated with reduced behavioural and neural (fMRI) sensitivity to bizarre facial expressions; this may be due to disturbed control of emotion-related face processing in the fusiform gyrus by the amygdala and prefrontal cortex

On fMRI scz had deficit in amygdala reactivity to negative face stimuli and an alteration (correlated with antipsychotic drug dosage) in functional coupling between amygdala and subgenual cingulate; well siblings were similar to controls; this suggests that this problem is not a heritable phenotype but rather an effect of treatment

Using fMRI and a continuous performance task authors found significant impairment in functional connectivity between dorsolateral PFC and task-relevant brain regions

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) both psychotic symptoms and neurocognitive deficits appeared to contribute independently to decreased quality of life in scz

Scz were more impaired on memory indices than were bipolar cases and the latter were mildly impaired compared to healthy controls; scz had smaller total cerebral volume and bigger ventricles; left amygdala volume was predictive of memory performance in both patient groups

Loss of effective associative learning in scz can be assessed by eye-blink conditioning processes and eye-blink conditioning improved at 2 and 24 hours following secretin¹¹⁴⁰ but not placebo, suggesting a possible role for secretin in the modulation of cerebellar-mediated classically conditioned learning

Mistakenly seeing anger in other people's expression is related to high suspiciousness and low self-esteem in scz

There may be a specific impairment of voluntary response inhibition in scz (stop-signal reaction time) – patients demonstrated intact involuntary response inhibition (masked priming task)

In a 15-year Chicago follow-up study, external locus of control was not specific to schizophrenia but was significantly associated with less recovery periods, to both depressed mood and psychosis, and, most importantly, to personality

People at high genetic risk for scz (N = 97) performed poorly on tests of spatial memory capacity and planning processing speed compared to controls (N = 25) even after controlling for IQ

Scz patients performed lexical decisions on target words that were semantically related and unrelated unconsciously perceived masked prime words: increased unconscious activation of several related concepts may interfere with conscious goal-directed thinking in those patients with formal thought disorder

Youth-onset scz is associated with severe cognitive deficits whereas late-onset scz is associated with specific deficits (e.g. attention, fluency, IQ, and visuospatial construction) that are not simply due to ageing

Compared with intellectually matched controls, first-episode scz/schizoaffective disorder is associated with multiple deficits in executive function, processing speed, and verbal memory

Scz patients who over learn verbal material bring compensatory brain areas in to action to make up for cortical inefficiency

Motivation is important in neurocognition, social cognition and functional outcome in scz

Whilst scz is associated with positive affect evaluation (pleasure) there is a problem translating this experience into motivation

¹¹³⁹ Maher's (1983) theory that associative processes are overdeveloped in schizophrenia, e.g. 'bees make honey' becomes 'bees make sweet'. (McKenna, 2007, p. 202)

¹¹⁴⁰ Secretin, which enjoyed a brief vogue in autism, is a hormonal agonist for the prototype group B G-protein-coupled receptors. (see Bolbecker et al., 2009)

Used Temperament and Character Inventory in Northern Finns born in 1966 who developed a psychotic disorder: reward dependence and persistence were significantly correlated with PANSS negative symptoms; higher P scores predicted higher social and occupational functioning, and higher harm avoidance predicted higher likelihood of being on disability pension

Regarding first episode psychosis, scz have severe, widespread neuropsychological impairments compared to other diagnostic groups

African Americans with schizophrenia or schizoaffective disorder were slower and more inaccurate when performing neurocognitive tests than their biological relatives, the latter doing less well than community comparison subjects; there were significant heritabilities for most neurocognitive domains (especially abstraction/flexibility, verbal memory, face memory, spatial processing, and attention speed)

Premorbid adjustment before first psychotic episode influences severity, but not form, of cognitive dysfunction

When effects of general impairment of intellect are reduced (by using scz patients who were relatively free of this problem) there was no deficit in identifying facial emotions but there may be difficulty to the intensity of such emotions; difficulty in recognising familial faces (not found on *Benton Facial Recognition Test*) may be a semantic memory problem

Scz had reduced working memory capacity but were similar to controls in precision of working memory representations

In a longitudinal study with 2.5-year follow-up, global neuropsychological functioning (NF) was equally impaired in individuals at high risk for schizophrenia or other psychoses (CHR) and family high-risk groups compared to controls; NF in CHR group was much lower in people who progressed to psychosis than in those who did not and was worst in the subgroup with a family history of psychosis; tests of processing speed and verbal and learning best discriminated CHR from controls; and worse verbal memory predicted more rapid conversion to psychosis

A meta-analysis of 70 studies (Aleman ea, 1999) showed that there is a stable but significant impairment of memory in schizophrenia that is unaffected by age, medication, illness duration, patient status, symptom severity, or positive symptoms, with negative symptoms having a small but significant effect. Another meta-analysis of 187 studies (Forbes ea, 2009) found working memory deficits in schizophrenia patients and that these could not be simply explained by any current IQ differences between patients and controls. Barrett ea (2009) found that first-episode bipolar disorder and schizophrenia subjects, relative to healthy controls, were most impaired in terms of memory, executive function and language but bipolar patients performed much better on tests of response inhibition, verbal fluency and callosal function; and the differences could be explained by the greater likelihood of schizophrenia cases to be globally impaired and to have negative symptoms.

Negative symptoms (subtractions from behaviour and emotion) may be a primary feature of schizophrenia (e.g. social withdrawal, blunted affect, and avolition) or be secondary to positive symptoms like depression or paranoid delusions. The idea that they are confined to 'burned out' cases has been abandoned; anyway, evidence for 'burn out' is weak at least. Nevertheless, there is some support for the idea that negative symptoms are less prominent in late-onset schizophrenia and more prominent in early-onset cases that have grown old. Schizophrenic patients tend to be less concerned by their negative symptoms than are depressives. Negative symptoms might result from (or made worse by) environmental deprivation, although this is disputed, (Phillips ea, 1991; Curson ea, 1992) or EPS. Negative symptoms may be less common in Nigerian schizophrenics. The relatives of patients with mainly negative symptoms may be at less risk for schizophrenia than is the case in other circumstances. (Baron ea, 1992) However, other work (Malaspina ea, 2000) has suggested that schizophrenia in association with a positive family history is associated with particularly treatment-resistant negative symptoms but not especially with deficit syndrome (DS: described below), although the familiarity of DS is supported elsewhere. (Ross ea, 2000) The *clinical poverty syndrome*, which is not specific to schizophrenia, consists of withdrawal, social isolation, flattening of affect, poverty of speech and ideation, and lack of drive or motivation. Johnstone and Frith (1996) divided schizophrenia into three dimensions ('poverty', 'hallucinations and delusions', 'disorganisation') based on principal component analysis. Mayerhoff ea (1994) reported their findings in first episode cases in remission from positive schizophrenic symptoms. Four percent had the full *deficit syndrome* (DS; *restricted affect, reduced emotional range, diminished speech, curbing of interests, reduced sense of purpose, and decreased social drives*), 19% had some deficit symptoms, and 77% had no deficit symptoms. Those patients in the last group had better premorbid functioning and a better global outcome than did patients with deficit symptoms. The *neuroleptic-induced deficit syndrome* (NIDS) is said to resemble the negative symptoms of schizophrenia but clears when medication is stopped, whereas primary schizophrenic DS tends to remain stable. It is said that atypical antipsychotic drugs (olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone) are less prone to induce NIDS. A patient's negative symptoms may

be exacerbated by D2 blockade, possibly by downregulation of prefrontal D1 receptors¹¹⁴¹. There is still some debate as to whether atypicals like clozapine are effective against primary as distinct from negative symptoms¹¹⁴². (Miyamoto ea, 2003, p. 461; Cunningham Owens, 2004, p. 269; Harvey ea, 2005) The same can be said for using anticholinergic drugs, which also have known detrimental effects on cognitive function.

A number of authors, including Frith and Done (1988), attributed positive symptoms (e.g. alien control) to a defect in the internal monitoring of action, (Johns ea, 2006) and negative symptoms to a defect in the initiation of action by the brain. There might be a DA deficiency in the prefrontal cortex, excess blockade of 5-HT_{2A} receptors by serotonin, or excitotoxicity from excess glutamate.

In pseudoneurotic schizophrenia, described by Hoch and Polatin in 1949, a diagnosis that is basically redundant, the presentation consists of neurotic symptoms, the patient being mistaken initially as having a 'neurosis'. Close scrutiny may reveal evidence of schizophrenia. The patient is very anxious but the normal therapies for this are disappointing. Some authors would hold that Hoch and Polatin were actually describing borderline personality disorder.

The presence of excess 'soft' (*minor*¹¹⁴³) *neurological signs* (SNS) unrelated to medication (Dazzan & Murray, 2002) in schizophrenia has attracted much attention, as has suggestions that they may be mainly left-sided. Examples of SNS include poor motor sequencing/co-ordination, right-left discrimination, and sensory integration difficulties. Hard signs, on the other hand, are localisable to specific brain regions and typically involve motor or perceptual systems. The borderland between soft and hard signs is difficult to follow in the literature, e.g. early-onset schizophrenia has been found to be accompanied by an excess of choreiform movements and corticospinal tract signs that persist over time. Are these soft or hard?

Polydactyly may be over-represented in patients with familial schizophrenia. In comparison with normals and psychiatric controls, left- and mixed- handedness are significantly more common in schizophrenia. Mixed handedness may be associated with more neurological impairment¹¹⁴⁴, and a history of poor scholastic attainment and poor premorbid adjustment. Dragovic ea (2005) found that leftward reversal (shift to left in behavioural lateralisation) rather than reduced lateralisation was associated with clinical severity and neurocognitive deficits in schizophrenic patients. The head circumference of long-stay schizophrenic patients and at birth in those later to develop the illness has been found to be pathologically small by some but not all researchers. There have been reports of facial anomalies in schizophrenia in the form of an overall narrowing and elongation of the mid- and lower face. (Lane ea, 1997; contrast these findings with McGrath ea, 2002, e.g. smaller glabella to subnasal height) Minor hand and mouth anomalies, together with anomalies of the face, may be commoner in schizophrenics and their siblings than in the general population, (Egan ea, 2001) but the members of the same family do not necessarily have the same anomalies. (Ismail ea, 1998) Male schizophrenics may have shorter stature than healthy comparators. (Nopoulos ea, 1998) Kinney ea (1986) reported that the prevalence of neurological abnormalities in the relatives of schizophrenics was significantly greater than in controls, but similar to that among the schizophrenics. Relatives and controls differed even more markedly on signs involving motor system abnormalities of localising significance. Similar findings have been recorded by others workers. (see O'Shea, 1997) Schubert and McNeil (2004) found more soft signs, involuntary movements, and cranial nerve abnormalities among the offspring of women with schizophrenia, whereas the offspring of women with affective psychosis had no such excess. There are many methodological flaws in research into SNS. They are found in other psychiatric disorders (e.g. mood disorders – see Goswami ea, 2007; Lloyd ea, 2008¹¹⁴⁵), their relationship to aetiology is unclear, and the literature is conflicting regarding findings. Lawrie ea (2001) consider soft signs and minor physical anomalies to be non-genetic, non-specific markers of developmental deviance. Leask ea (2002) could not link soft signs to infectious illnesses. Whitty ea (2003) concluded that motor and cortical signs were state-dependent whereas 'harder' signs were more static. Bachmann ea (2005) found that the level of soft signs varies with illness course in first-episode

¹¹⁴¹ Hirvonen ea (2006) looked at twins discordant for schizophrenia and found that high D1 receptor density in medial prefrontal cortex, superior temporal gyrus, and angular gyrus was associated with increasing genetic risk for schizophrenia and that D1 receptor binding showed widespread reduction in medicated schizophrenic patients.

¹¹⁴² Kumra ea (2008) found that children with early-onset schizophrenia who were resistant or intolerant to at least two antipsychotics responded better (including negative symptoms) to clozapine than to olanzapine (up to 30 mg/day) in a randomised, comparative trial.

¹¹⁴³ Do not localise to tract or nuclear lesion. Both groups developed significant metabolic problems.

¹¹⁴⁴ Mixed handedness is increased in combined schizophrenia and intellectual disability. (Hemmings & Bouras, 2007, p. 205)

¹¹⁴⁵ Lloyd ea (2008) suggest that these anomalies occur during the first trimester.

schizophrenia but that the level remains steady in comparison subjects. Also, predictors of soft sign scores at follow-up were soft sign levels at remission and compliance with treatment. It should be noted that minor physical anomalies are very common in the normal population. (Lane et al, 1997) A total physical anomalies score on the *Lane Scale* (Lane et al, 1997) in first-episode psychosis was associated with grey matter reduction in prefrontal cortex and precuneus and grey matter excess in basal ganglia, thalamus and lingual gyrus. (Dean et al, 2006) MRI in 70 adolescents aged less than 18 years who had positive psychotic symptoms for under 6 months revealed that increased severity of sensory integration SNS had smaller thalamic bilaterally whereas those with more severe sequencing of complex motor acts SNS had a smaller right caudate nucleus. (Janssen et al, 2009) Dazzan et al (2008), in a controlled study, suggested that SNS were specific to psychosis. However, the comparison was between psychoses and 'normals' (general population), so other diagnoses were not tested.

Biswas et al (2007) looked at SNS in outpatients with schizophrenia diagnosed according to WHO diagnostic research criteria in India. Some findings are shown in the table. The earlier the onset of psychosis the more frequent and severe were the SNS and the more severe was the psychopathology; there was no relationship between SNS and dose or type of antipsychotic medication; and there was no correlation between duration of illness and SNS. There was a positive association between lower educational status and lower IQ (especially in the two younger onset groups) and more SNS, suggesting to the researchers that neurodevelopmental abnormalities predate overt psychosis onset.

Ruiz-Veguilla et al (2008) examined 92 cases of first episode 'functional' psychosis (87% non-affective) and found SNS had a significant independent association with not having been a heavy cannabis user¹¹⁴⁶, having a family history of psychosis, male sex, lower score in verbal fluency and higher score in negative symptoms.

Thomann et al (2009) looked at brain changes underlying SNS in schizophrenia and in healthy controls. MRI showed reduced grey or white matter densities in pre- and post-central gyrus, pre-motor area, middle and inferior frontal gyri, cerebellum, caudate nucleus, and thalamus in subjects with schizophrenia. The only association with SNS in the controls was reduced densities in frontal gyri. These findings supported the notion of cognitive dysmetria¹¹⁴⁷ with disruption of the cortico-cerebellar-thalamo-cortical circuit in schizophrenia.

Neurological soft signs (SNS) in India

Biswas et al (2007)

Numbers: 15 with onset < 14 years of age: childhood-onset, 20 with onset > 14 and < 18 years: adolescent onset, 20 with onset > 18 years (adult onset)

SNS frequency: 100% in childhood onset cases, 90% in adolescence onset cases, 55% in adult onset cases

Goswami et al (2007)

Used modified Kolakowska battery (maximum score = 42) for SNS on 53 euthymic bipolar affective disorder (BAD) patients and controls: SNS increased slowly and significantly with age in controls (average score = 2.8) but BAD cases had high scores (average score = 8, i.e. lower than reported in schizophrenia) throughout age range that were not age related (do not get worse)

Spontaneous dyskinesias unrelated to medication have been known to occur in schizophrenia since the time of Kraepelin. There is some evidence that Parkinsonism, not attributable to medication, may be part of the schizophrenia spectrum, e.g. a greater tendency to right over left sided signs could be interpreted as indicating left striatal hypodopaminergia. (Caligiuri et al, 1993; McCreadie et al, 2002b) In fact, Parkinsonism had been described by Kraepelin in dementia praecox in 1919. Rosso et al (2000) followed up Philadelphia children during their first 7 years of life and found that at ages 4 and 7 years tremor, tics, spasms, or athetosis were significantly overrepresented in those later diagnosed with DSM-IV schizophrenia. Walker et al (1994) compared childhood home movies of DSM-III-R schizophrenics, their siblings, and normal controls and found an excess of motor abnormalities in the patient group (choreoathetosis, abnormal posture [e.g. of the hand], and a tendency to move a body part when the contralateral part was called into action).

¹¹⁴⁶ Does this mean that cannabis protects against SNS or that cannabis causes psychosis without SNS?

¹¹⁴⁷ Abnormal connectivity may underlie psychopathology.

Different mechanisms may underlie brain dysfunction in familial and sporadic cases of schizophrenia, with an excess of 'primary' problems (e.g. cranial nerve signs, frontal release signs) in sporadic cases and 'integrative' (depending on integration within and between motor and sensory systems) problems (e.g. astereognosis) in familial cases.(Griffiths ea, 1998)

Three syndromes of schizophrenia (Liddle & Barnes, 1990)

Psychomotor poverty - poverty of speech, flat affect

Disorganisation - formal¹¹⁴⁸ thought disorder, inappropriate affect

Reality distortion - delusions and hallucinations

The *psychomotor poverty syndrome* (PPS) consists of reduced spontaneous movement, poverty of speech, flat affect, reduced cerebral perfusion in the left prefrontal cortex, and impaired neuropsychological testing of frontal lobe function, perhaps with low levels of the DA metabolite homovanillic acid in the CSF. A wide range of psychotic disorders are associated with impaired ability to distinguish between fragrances, even when the psychosis is brought under control.(Brewer ea, 2001; Good ea, 2006) Such *olfactory* identification deficits are found in both treated and neuroleptic-naïve schizophrenics as well as, in some but not all studies (Compton & Chien, 2008), in their well relatives.(e.g. Kopala ea, 2001; Turetsky ea, 2008; Turetsky & Moberg, 2009) Malaspina and Coleman(2003) found that olfactory identification deficits in schizophrenia were related to negative symptoms and the deficit syndrome and that both relationships could be explained by an association of olfactory identification deficits with diminished social drive. Male patients may have impaired assignment of pleasantness to amyl acetate, an effect that seems to independent of smoking status.(Moberg ea, 2003) People at very high risk for developing schizophrenia because of attenuated or brief psychotic symptoms or loaded family histories may have impaired olfactory identification ability.(Brewer ea, 2003) A finding of smaller posterior nasal volumes in schizophrenia has been interpreted as indicating a specific developmental cranio-facial abnormality.(Moberg ea, 2004) Olfactory structures develop in conjunction with the palate and ventral forebrain. Using MRI, Turetsky ea (2009) found shallow olfactory sulci in schizophrenic subjects compared with normal controls (N = 36 and 28 respectively). The authors suggested that this finding may be a marker of early disruption of embryonic development.

Self-blinding¹¹⁴⁹

Many causes, e.g. schizophrenia, TLE, drug misuse (e.g. LSD), encephalitis, diabetes

May represent a failed suicide act

Autoenucleation is usually carried out with the fingers

Patient may be left with a temporal hemianopia in the surviving eye (traction on optic chiasma)

Children with severe, early onset bilateral retinal disease (e.g. CMV retinitis) may poke the eye in order to produce visual sparks or *phosphenes* - this activity has been misinterpreted as either badness or autism

Autocastration

Reported in paranoid schizophrenia and in personality disordered chronic transsexuals with a history of self-mutilation

Psychotic denial of pregnancy (O'Shea, 2000c)

Rare

Associated with schizophrenia, history of loss of custody of children, fear of loss of future custody - carries risks of poor prenatal care, violence to the foetus or newborn,¹¹⁵⁰ and unassisted delivery

Depression in schizophrenia: Affective symptoms are common in schizophrenia and depression is a common reason for attempted suicide in these patients. This must not be confused with neuroleptic-induced Parkinsonism. However, when drug-induced Parkinsonism is misdiagnosed as depression and treated with tricyclic antidepressants (TCAs) the patient often improves because these drugs are anticholinergic! Also,

¹¹⁴⁸ I.e. structure, organisation, and coherence of thinking.

¹¹⁴⁹ The mythology of self-inflicted eye injuries goes back to Odin, a Norse god, and Oedipus. Self-blinding is recommended by St Matthew (chapter 5, v. 29) for sinful thoughts.

¹¹⁵⁰ Including poor nutrition and self-induction of labour.

dysphoria is commonly associated with akathisia. The notion of post-psychotic depression is an old one.¹¹⁵¹ Psychosocial factors might be important here but studies have failed to support an increase in depression following recovery.(e.g. Koreen ea, 1993) Indeed, depression is common early in the course of schizophrenia, and has been shown to correlate with positive symptoms. Also, Simms and Mulholland (2008) failed to link depression in schizophrenia to perceived lack of social support. Many schizophrenic patients who are taking their medication complain of being 'trapped' or of feeling vaguely unwell. Many researchers believe that that depression is an integral part of schizophrenia. It may be that dysphoric symptoms precede, coincide with (during which they may be masked), and follow the more florid illness. Whether this is due to a functional link between the two symptomatologies or due to a common physiological disturbance is still disputed. Treatments for these depressive symptoms include cognitive therapy, antidepressant drugs¹¹⁵², neuroleptics and, if necessary, electroconvulsive therapy (ECT). The term 'revealed' depression simply infers that the depression was revealed by treating the florid symptoms. Some authors hold that verbal memory impairment in schizophrenia is explained by depression and that it is not an integral part of the disorder.(Brébion ea, 2001)

Manic symptoms in schizophrenia: Experienced clinicians know of a few patients with long histories of undoubted schizophrenia that have episodes of superimposed manic and hypomanic symptoms. Depending on how one defines such symptoms, 3-10% of cases may experience such episodes at some stage.(Häfner & an der Heiden, 2003, p. 122) The rare patient appears chronically elated. How to fit them into the nosology is difficult to say. Even when one considers bipolar disorder, schizoaffective disorder, drug-induced disorder¹¹⁵³, and somatic disorders (e.g. neoplasia) one is left with the above residuum.

Schizophrenia in patients with intellectual disability (ID): Schizophrenia may be more common in this patient group than in the general population.(Reid, 1993) It may not be possible in individual cases to refine diagnosis beyond 'psychosis not otherwise specified'. Brief psychotic episodes may follow stress¹¹⁵⁴. When one is dealing with cases with mild ID and relatively good verbal ability then there is little difference from people in the normal range of IQ in terms of clinical features apart from simple, concrete reporting of delusions. Questions must be understood, e.g. asking someone with a low IQ about 'hearing or seeing things' may be interpreted as 'can you hear and see?' Relatives may be able to distinguish change from the usual poor verbalisation to delusions. With lower IQ levels observation becomes more important for diagnosis than verbal interaction.

Diet and schizophrenia: Schizophrenic patients smoke heavily, are often overweight¹¹⁵⁵ or obese, eat too much saturated fat, have a low intake of antioxidants, and eat too little fruit and vegetable.(McCreadie, 2003) Their diet is low in Vitamin E relative to cholesterol.(McCreadie ea, 1998; Scottish Schizophrenia Research Group, 2000) According to Peet,(2004) a higher national intake of refined sugar and dairy products predicted a worse two-year outcome of schizophrenia. This may be aetiologically relevant or an example of ecological fallacy.(McIntosh & Lawrie, 2004) Correlation does not necessarily equal causation and interventions need to be sustained.(McCreadie ea, 2005)

Substance misuse in schizophrenia:

- Up to 65% of patients with schizophrenia have lifetime diagnoses of substance use disorders (Mueser ea, 1990)
- 15% -60% of patients with schizophrenia in America abuse psychoactive drugs (Dixon ea, 1991)

¹¹⁵¹ And not uncommonly reported in treated delusional disorder.(Munro, 1999) Indeed, it was recognised as early as 1920, long before the advent of antipsychotic drugs.(Goff & Shader, 2003, p. 574)

¹¹⁵² Which often fail to work (Johnson, 1981) and which can potentially exacerbate psychosis.(APA, 2002, p. 425) However, Siris & Bench (2003, p. 151) wonder if the treatment of depressive symptoms during psychotic decompensation has led to an erroneous attribution of psychogenicity to antidepressant drugs.

¹¹⁵³ In DSM-IV terms, by determining that the mental disorder came before the substance use disorder or lasted for 4 or more weeks following cessation of substance use.

¹¹⁵⁴ Stress here refers to what someone with ID finds stressful, which may not be so for people with greater intellectual ability.

¹¹⁵⁵ Whilst early weight increase is typically associated with atypical antipsychotic drugs typical agents may be associated with similar increases in the longer term.(Perez-Iglesias ea, 2008) Not all (particularly abdominal) **obesity** in schizophrenia appears to be related to antipsychotic drugs, education, diet or smoking.(Saarni ea, 2009) Patients with affective psychosis do not appear to share this problem.(Saarni ea, 2009)

- The combination of drug misuse and schizophrenia is associated with male sex, homelessness, excess psychotic symptoms, non-adherence to treatment, poor prognosis, violence and aggression (Soyka, 2000)
- Young and male patients are the main users in central London (Duke ea, 2001)
- First-episode schizophrenia patients in West London who persistently use substances have worse positive and depressive symptoms but not negative symptoms (Harrison ea, 2008)
- First-episode schizophrenia patients are less likely to adhere to medication or to stay in treatment if they use cannabis (Miller ea, 2009)
- First-episode psychosis cases in Northern Ireland who persist with substance misuse have more severe depression, more positive symptoms, poorer functional outcome, and a greater relapse rate at one year compared to patients who stop such misuse after presentation and those with no history of misuse, with no difference in outcome between patients who stop such misuse and those with no history of misuse (Turkington ea, 2009)

Drug abusing patients are more likely to be hostile, commit offences, and commit suicide. Duke ea (2001) found high use of cannabis, psychostimulants, LSD, opiates, and anticholinergics in central London. Veen ea (2004) reported a strong association between use of cannabis¹¹⁵⁶ and earlier age at first psychotic episode in males with schizophrenia. This research receives support from Barnes ea (2006) and Di Forti ea.(2009) Wade ea (2006), in a follow-up study of first-episode psychosis, found substance misuse increased risk of inpatient admission, relapse of positive symptoms¹¹⁵⁷ and shorter time to relapse of positive symptoms. Henquet ea (2005), in a prospective and population-based (Munich) sample, found that cannabis use in people aged 14 to 24 years moderately increased the risk for psychotic symptoms but had a much stronger effect in those with evidence of predisposition for psychosis. An increase in psychotic symptoms predicted relapse to cannabis abuse and medication adherence reduced cannabis relapse risk in a prospective post-discharge study of psychotic patients.(Hides ea, 2006) Arendt ea (2005), using the Danish Psychiatric Central Register, found an increased risk for later development of schizophrenia spectrum disorders in patients who had been treated for cannabis-induced psychosis; male gender and young age were associated with increased risk; and schizophrenia tended to commence at a relatively young age. Further work conducted by Arendt ea (2008) was suggestive of cannabis-induced psychosis being an early manifestation of schizophrenia rather than a distinct disorder. Barnett ea (2007) reported increased substance use in people with first-episode psychosis, age at first use of cannabis, cocaine, ecstasy and amphetamine being significantly associated with age at first psychotic symptoms. Moore ea (2007) performed a systematic review and concluded that cannabis increases risk of psychotic outcomes independent of confounding and transient psychotic effects. Miettunen ea (2008) found cannabis use to be associated with prodromal symptoms of psychosis in adolescence and Mata ea (2008) found that cannabis abuse was associated with impaired decision-making before onset of psychosis but could not determine direction of causality¹¹⁵⁸. Rais ea (2008), in a Dutch MRI study, found that first episode schizophrenia patients who use cannabis have a greater brain volume reduction over a five-year follow-up than do patients with schizophrenia who do not use cannabis.

Veling ea (2008b) conducted a study among non-Western immigrants to The Hague with first-episode schizophrenia. Cases used cannabis more often than their siblings or general hospital controls. Cannabis use predicted schizophrenia but genetic predisposition did not predict schizophrenia. Barkus and Lewis (2008) looked at repetitive users of cannabis and suggested that their results indicate that cannabis reveals

¹¹⁵⁶ Independent of cannabis use, levels of the endogenous cannabinoid **anandamide** were found to be elevated in the blood and CSF of patients with schizophrenia.(e.g. Giuffrida ea, 2004) However, Koethe ea al (2009) found that lower levels of anandamide in CSF were associated with greater likelihood of transition to psychosis from the prodromal state, making them suggest that the endocannabinoid system might protect against schizophrenia. Weiser and Noy (2005) suggest that, rather than cannabis causing schizophrenia, an abnormal endogenous cannabinoid system might be common to both schizophrenia and the tendency to use cannabis. Egan ea (2008) reported reduced cortical cannabinoid 1 receptor (CNR1) mRNA and protein expression in schizophrenia at autopsy – this might be secondary to reduced GABA neurotransmission in the dorsolateral prefrontal cortex. However, it should be borne in mind that CNR1 variants have been implicated in cannabis use and nicotine dependence.

¹¹⁵⁷ See also Malla ea.(2008)

¹¹⁵⁸ I.e. does cannabis cause impairment or does the impairment make a patient abuse cannabis?

an underlying vulnerability to psychosis in people with high schizotypal traits. Acute cannabis use induced psychotomimetic symptoms in people prone to psychosis in a study conducted by Mason ea.(2009)

Hospitalised first-episode psychosis patients (N = 109; Compton ea, 2009)

Cross-sectional retrospective design

Classifying by maximum frequency of cannabis or tobacco use (zero, ever, weekly, daily) before onset – no significant effect on risk of onset

Progression to daily use of cannabis or tobacco – increased risk of onset (F > M)

Key: N = number off individuals; M = male; F = male

Nordentoft and Hjorthøj (2007) suggest that about 800 cases of schizophrenia could be prevented annually in the UK if cannabis consumption ceased. Netski ea (2003, p. 168) are sceptical of theories of self-medication¹¹⁵⁹ by substances in schizophrenia and the findings of Aguilar ea (2005) in relation to nicotine dependence in schizophrenia did not offer support for a self-medication hypothesis. Henquet ea (2010) found that patients had an acute enhancement of mood and subacute hallucinations from cannabis and, again, they found no direct connection between cannabis use and attempts at self-medication.

Diagnostic criteria for schizophrenia

Schneider's First Rank Symptoms (FRS)¹¹⁶⁰ have high reliability in diagnosis, are poor predictors of outcome, and are of low specificity¹¹⁶¹. The heritability of FRS remains controversial.(Cardno ea, 2002) Mellor (1982) stated that third person hallucinations were the least discriminating of the FRS. Feighner's criteria pick up poor prognosis cases. Spitzer derived his *Research Diagnostic Criteria* from Feighner's criteria. The RDC require only a two-week history. A structured interview known as the SADS (Schedule of Affective Disorders and Schizophrenia) has been developed for use with the RDC.

Type I and Type II: TJ Crow, in 1981, divided schizophrenia into 2 types, I and II. One version reads as follows: the overlap between the two types conforms to the hebephrenic illness of the old classification; type I corresponds to 'paranoid', 'reactive' and 'good-prognosis' schizophrenia or to 'schizophreniform' psychosis, whereas type II cases conform to 'simple' schizophrenia or to the 'defect' state; type I can change into type II.; and type II can enter the overlap zone with hebephrenic features but it cannot become a true type I illness. From the most to the least common the order seems to be a mixture of the two types, type I, and type 2. The usefulness of this dichotomy has been questioned.

International diagnostic differences: In 1972 Cooper and his colleagues published the results of the US-UK Diagnostic Project. The concept of schizophrenia was shown to be very wide in New York. Under the same nosological rubric was subsumed the occasional manic, depressive, or personality disorder. In the UK, on the other hand, persons given the diagnosis of schizophrenia were more obviously suffering from the same syndrome. A year later, the WHO published the International Pilot Study of Schizophrenia in which they examined the diagnosis of schizophrenia in nine countries. Broad criteria were found in use in both the US and the USSR. However, if standard diagnostic methods were employed then one could still demonstrate a core of patients in all centres with similar symptomatology.¹¹⁶²

¹¹⁵⁹ The **cannabidiol** (CB1 antagonist) in cannabis may have antipsychotic properties, reduce dysphoria and quell anxiety but it is present in only small amounts in high-THC cannabis.(Atakan, 2008)

¹¹⁶⁰ FRS were published by Kurt Schneider.(1959: lived 1887-1967) although the individual symptoms were described long before that.(e.g. Haslam, 1810)

¹¹⁶¹ E.g. they may occur in as few as 20% of schizophrenic patients.(Ho ea, 2003, p. 388) They also occur in mania and depression. FRS can occur in organic mental disorders, especially if consciousness is not impaired, and particularly in post-ictal epileptic psychosis or alcoholic hallucinosis. The frequency of FRSs in schizophrenia ranges from 28 - 72%. This variation may be due to the diagnostic criteria used and the methods employed in eliciting FRS. However, FRSs occur much more commonly in schizophrenia than in other psychiatric disorders.

¹¹⁶² It should be borne in mind that there are wide intra-national differences also, e.g. Washington v New York and Leningrad v Moscow. In like manner there are some individuals who hold extreme views, e.g. Szasz holds that mental illness is a 'myth' and that schizophrenia is the 'sacred symbol of psychiatry'. At the Serbsky Institute in Moscow, Snezhnevsky offered a broad concept of schizophrenia - many eccentrics and personality-disordered individuals were included in his idea of schizophrenia. Snezhnevsky took more cognisance of the course of the illness than of the manifestations. He divided the disorder into the following: (a) 'continuous', (b) 'periodic', (c) a mixture of (a) and (b) 'shift-like'. The Russian concept of 'sluggish' schizophrenia has been attacked as being a political abuse of psychiatry. 'You'd want to be mad to be a dissident'.

Prognosis in schizophrenia

'The symptom patterns conventionally diagnosed as schizophrenia and regarded as reliable produce a rather heterogeneous spectrum of illness courses'. (Häfner & an der Heiden, 2003, p. 113)

'Schizophrenic illness remains heterogeneous with regard to illness course and outcome even when narrowly diagnosed with the help of modern operationalized diagnostic criteria'. (Modestin ea, 2003) 'When workers are in short supply, the burden of illness expands to include the lost labour potential; in hard times, concern is more focused on the cost of care'. (Warner, 2003)

'There is a marked heterogeneity in the outcomes of schizophrenia, depending on the domain considered'. (Ruggeri ea, 2004)

There are about 150,000 cases of schizophrenia at any one time in the UK. Hegarty ea (1994) reported that only 40% of subjects could be considered to have improved after follow up averaging 5.6 years during the century spanning 1895-1992. Outcome was better with broad or undefined criteria, but poorer (27%) with narrow criteria. Outcome varied for different reasons (treatment, criteria changes) at different times. In the closing years of the 19th century Kraepelin viewed schizophrenia as a disorder which always carried a poor prognosis. In the 1960s Brown and others found that after five years 56% of discharged schizophrenics made a social recovery, 35% were socially damaged but lived outside hospital, and only 11% had spent all their time in hospital. Bland and Orn (1978) found that after fourteen years about half were coping well with minimal disability, one-quarter had moderate to marked disability and a further quarter were disabled psychiatrically, socially and occupationally. Manfred Bleuler (in 1974, lived 1903-94) followed up 208 patients for over twenty years and found that there was usually no further deterioration after five years; in fact, some even improved. The WHO found that Third World schizophrenics had a relatively good outcome - one wonders if these cases were not different illnesses with an acute onset, (McCabe, 1976; Häfner & an der Heiden, 2003, p. 130) whether they had a more accepting society, or whether the pace of life had an ameliorating effect on them. Also, there have been reports of a relatively good outcome for schizophrenia in some industrialised societies (Prague, Nottingham) and of a poor outcome in Cali. Singh ea (2004) found that 19% of first episode psychosis identified in Nottingham between 1992 and 1994 received an intake diagnosis of acute and transient psychotic disorder (ATPD: ICD-10 F23). They concluded that ATPD identifies a heterogeneous group of disorders in which diagnostic stability was confined to females. Three-year outcomes were similar to that of affective psychosis and significantly superior to that of schizophrenia. Also, in non-affective psychotic disorders, being a woman and having good premorbid function, but not acute onset or early remission, predicts favourable outcome at three years. Pillman and Marneros, (2005) in a study that consisted of 76% females, found a much better prognosis for ATPD than for 'positive' schizophrenia: 31% v 0% respectively were functioning well without medication at the end of the follow up period. Sikanerty and Eaton (1984) reported a lower prevalence for schizophrenia in the Third World. However, Stevens (1987) was sceptical about what diagnosis one was dealing with. There are also reports from developing countries of symptomatic, severely disabled chronic, untreated patients living with extended families. (Padmavathi ea, 1998) Interestingly, African Americans are at risk of misdiagnosis for schizophrenia in the presence of affective or organic¹¹⁶³ brain disorders. (APA, p. 428)

Prognosis in first episode acute schizophrenia¹¹⁶⁴

Average duration of acute episode = 8 to 12 weeks (but undetected for 2 to 3 years)

25% achieve full, permanent recovery

50% relapse without progression to chronicity

25% experience recurrent relapses with deterioration of personality deterioration, and impaired social function and behaviour

Therefore, 75% (at least) are at risk of relapse

Prognosis in first episode non-affective psychosis (Crumlish ea, 2009)

118 consecutive referrals¹¹⁶⁵ prospectively followed up

Negative and disorganised symptoms improved between 4 and 8 years

DUP¹¹⁶⁶ predicted remission, positive symptoms and social function at 8 years

¹¹⁶³ One rarely sees a patient who, on recovering from delirium, persists in believing that his hallucinatory experiences were based in reality. (David, 2009, p. 11)

¹¹⁶⁴ Figures vary greatly depending on study quoted, time study was conducted, and criteria used, e.g. DSM-IV-TR criteria for schizophrenia define a narrow disorder with perhaps 10% having only a single episode with full recovery. Early improvement on the PANSS total score (30% or more at week 2) appears to be associated with response/remission in first-episode cases. (Schennach-Wolff ea, 2010)

¹¹⁶⁵ St John of God service, South Dublin.

DUI predicted continuing functional recovery between 4 and 8 years
Suggests that there is an early critical period of deterioration

Brockington ea (1978) used ten different occupational definitions of schizophrenia and compared them to determine their efficacy in predicting the long-term outcome. The RDC was found to be best at identifying the poor prognostic group. Even the best studies fail to predict more than one-quarter of the variation in subsequent course.

Wing and Brown (1970) looked at the long-stay schizophrenic patients of three different hospitals. The hospitals with the most barren, understimulating wards had the most withdrawn, silent and affectively blunted cases.

Prognosis

Although readers of the literature will be well aware that not all research finding agree it can be argued that, in general, a:

Good prognosis is associated with

Living in a developing country¹¹⁶⁷

Female sex

Married status

Good social and occupational adjustment

Adverse life events

Substance-induced

Affective symptoms¹¹⁶⁸

Acute onset

Low familial loading seems to be associated with later onset and better outcome

Poor prognosis is associated with:

Male sex

Low social class

Living in a developed country

Low IQ, cognitive dysfunction

Childhood problems e.g. difficulties in learning

Poor medication response¹¹⁶⁹ or compliance

Insidious onset

Long duration of untreated psychosis (DUP) or untreated prodrome (Fusar-Poli ea, 2009)

Negative symptoms

Poor preservation of affect

Lack of depression

Excited state

Family history of schizophrenia¹¹⁷⁰

Poor insight

Poor premorbid adjustment¹¹⁷¹ (non-socialising, no relationships, poor work record)

High levels of EE (expressed emotion) in the family

Large cerebral ventricles

Abnormal MRI or EEG

Early onset

¹¹⁶⁶ **DUP** = duration of untreated psychosis; **DUI** = duration of untreated illness = duration of **prodrome** (start of prodromal symptoms to start of psychosis) + DUP.

¹¹⁶⁷ But not all studies agree, e.g. Mojtabai ea(2001) and Ran ea.(2001)

¹¹⁶⁸ In self or family.

¹¹⁶⁹ A naturalistic sample of inpatients (N = 247) with ICD-10 schizophrenia (Jäger ea, 2009) found that 27% and 54% were in remission (defined as at least a 40% reduction in total PANNS score from admission to discharge) at week 2 and on discharge respectively; a 20% reduction in total PANNS score within 2 weeks predicted remission and a 30% reduction predicted response.

¹¹⁷⁰ A few researchers found the opposite.

¹¹⁷¹ Rabinowitz ea(2006) found good premorbid functioning in first episode psychosis to be associated with better treatment response and less extrapyramidal symptoms.

Cognitive dysfunction is a major determinant of outlook.(Stahl, 2003) Milev ea (2005) found verbal memory predicted impairment in recreational activities, negative symptoms and memory predicted relationship impairment, and attention and negative symptoms predicted work performance, findings broadly similar to those of Kopelowicz ea.(2005) Brodaty ea,(2003) in a small study with methodological shortcomings¹¹⁷², suggested that late-onset schizophrenia might be a prodrome of Alzheimer's disease. While this was not borne out by a cross-sectional study conducted by Eyler Zorrilla ea (2000) it received support from a study showing an increased risk of developing dementia compared to patients with osteoarthritis and to the general population.(Kørner ea, 2008) Ciompi (1980) performed an average 37-year follow-up of 1,642 patients with a diagnosis of schizophrenia from the start of the century to 1962. One-third had a good to fair social outcome. The symptoms often became less severe in later life. However, more recent studies suggest that elderly schizophrenics remain symptomatic and impaired.(Eyler Zorrilla ea, 2000; Jeste ea, 2003) Early onset may be associated with neuroleptic-resistance.(Meltzer ea, 1997) Symptom dimensions may tell us more about prognosis than can diagnostic categories. In a London WHO study (Prudo & Blum, 1987), after a five-year follow-up of 100 schizophrenics, 49% had a good symptomatic outcome, and 42% had a good social outcome. Poor social functioning at the start of the study predicted a poor symptomatic outcome. Mason ea (1995) performed a 13-year follow-up of Nottingham first episode ICD-9 schizophrenia cases. Four were lost to follow up and 5 had died. Fifty-two percent had no psychiatric symptoms in the previous two years, 52% had no negative symptoms, 55% had good to fair social functioning, and only 17% were fully well, symptomless, and off treatment. The same authors later reported that the course may be stormiest at the start but tends to plateau later, with no progression or alleviation in the long run. Finnerty ea(2002) were able to follow up only 37 of 67 (55%) first episode schizophrenic patients over 15 years: 43% (of the 55%) were more or less continuously psychotic, a similar percentage suffered recurrent episodes of their disorder, two out of three had moderate to severe symptoms for most of the time, over four-fifths were unemployed, and there had been eight deaths (6 male and 2 female; 5 suicides or 11% of the 55%; 3 from natural causes), the excess mortality being due to male deaths. According to Casey and Hansen,(2003, p. 18) the suicide rate in schizophrenia may have increased as a result of the move from chronic institutional life to 'less intensive treatment emphasising outpatient care'. While Healy ea (2006) reported a rise in the suicide rate associated with schizophrenia, Danish workers reported a fall.(Nordentoft ea, 2004) Finnish workers (Joukamaa ea, 2006) found an association between mortality and the neuroleptics used at baseline: is this an indictment of polypharmacy¹¹⁷³ or some other aspect of care or of illness severity?(see Healy, 2006) However, Tiihonen ea (2006) in Finland found that excess mortality was highest in patients not taking antipsychotic drugs¹¹⁷⁴.

Women have a better prognosis than do men in schizophrenia. This might be due to dopamine blockade by oestrogens; and higher blood oestrogen levels in schizophrenic women are associated with better cognitive ability.(Hoff ea, 2001) Women respond better to medication, family interventions, and are more compliant with treatment than are men; women may experience exacerbation of schizophrenia before or after menses are postpartum; and schizophrenia has a delayed onset in women. (Late-onset cases are more likely of paranoid subtype, never married and with a better work record.) Whilst results with exogenous oestrogens or anovulants have been mixed, there is some evidence that adjunctive oestrogens reduce psychotic symptoms.(Kulkarni ea, 2008)

There is some evidence that patients diagnosed before the advent of antipsychotic drugs ended up with greater deficits than those who diagnosed during the phenothiazine era.(McCreadie ea, 1991) Some authors have speculated that the illness has become milder over the years. Over 50% of schizophrenic patients will relapse during the first 9 months after stopping medication (compared to 16% in those remaining on medication), the great majority will have done so after 2 years¹¹⁷⁵.

¹¹⁷² Attrition of cases, poor cognitive performance at baseline, and no necropsy.

¹¹⁷³ The practice of polypharmacy (e.g. more than one second generation antipsychotic drug) and high dose regimens are persistent.(Tungaraza ea, 2010) Whilst such approaches may make some sense in individual cases it is important that the rationale for such decisions are documented in the clinical file.

¹¹⁷⁴ The same follow-up study of first admissions found hospitalisation and discontinuation were reduced by perphenazine depot, clozapine and olanzapine compared to haloperidol.

¹¹⁷⁵ Different authors give slightly different figures and follow up periods, e.g. fivefold increase in risk of relapse after stopping medication, with earlier relapse in those with poorer premorbid adaptation to school and social withdrawal.

Readmission rates are increased in those with more prior admissions and brief periods outside hospital between admissions and by shorter periods in hospital.(O'Shea, 1997) Such rates are also increased by non-adherence to antipsychotic drug therapy.(Knapp ea, 2004)

Allebeck and Wistedt (1986), in Sweden, performed a mortality study on 1,190 patients with a discharge diagnosis of schizophrenia during 1971. They identified all deaths through 1981. The schizophrenics had about twice the overall mortality of the general population. The excess mortality was found in all causes of death, but it was particularly high in 'unnatural death'. The suicide mortality was about ten times higher among male patients and eighteen times higher among female patients than in the general population.

Females with schizophrenia may be more suicide-prone if single and living alone, or if depressed. Some authors report equal suicide mortality for both sexes. Other work from Sweden and England has confirmed the increased mortality in schizophrenia from all causes, including suicide, cardiovascular disease, digestive disorders, endocrine conditions, nervous and respiratory diseases, undetermined causes and violence. Heavy smoking, poor diet, lack of exercise and obesity must be important in these cases.

Suicide in schizophrenia can occur at any stage of the illness. Most schizophrenic suicides have made prior suicide attempts. A recent systematic review (Hawton ea, 2005) found that risk of suicide in people with schizophrenia is strongly associated with depression, previous suicide attempts, substance misuse, agitation/motor restlessness, fear of mental disintegration, poor treatment adherence, and recent loss, and less so with active psychotic features. Methods are often violent, e.g. throwing oneself under a train.

Prediction is very difficult and prevention is best approached generally.(Kelleher ea, 1998; O'Shea ea, 2000) Many methodological factors interfere with the extraction of predictive factors from published studies, e.g. publication bias, different researchers looking at different risk factors, robustness of cohort design, and confounding factors.

Suicide in schizophrenia: risk factors

Male sex
 Young age
 Early onset of illness
 Early stages of illness
 Severe illness
 Recurrent relapses
 Command hallucinations
 Bizarre delusions
 Akathisia
 Anorexia or weight loss
 Excess alcohol intake or substance abuse
 Co-existent depression
 Hopelessness
 Social isolation
 Loss of job or being unemployed
 Fear of deterioration (higher IQ, current failure despite earlier academic success)
 Other negative life events, stress (? high EE)
 Return of insight
 Less than 3 months since discharge from hospital
 Spending a relatively short period in hospital
 Being on leave from hospital
 Communicating feelings of loneliness

Estimates of attempted suicide rates among schizophrenic patients vary from 18%-55%.(Siris & Bench, 2003, p. 152) Schizophrenics who attempt suicide tend to use lethal methods, to have high suicidal intent, and are often depressed. Suicide and accidents, together with other causes of death, account for an increased mortality rate in schizophrenia. Although suicide is an important cause of death in schizophrenia, the main source of excess mortality derives from natural causes,(Casey & Hansen, 2003, p. 21) especially cardiovascular, respiratory, and endocrine (esp. diabetes mellitus) diseases. According to Meyer,(2003, p. 63) the prevalence of diabetes in schizophrenia is about double that in the general population, a problem

compounded by low potency typical and certain typical antipsychotic drugs. However, the retrospective nature of most research suggests that diabetes may be intrinsic to schizophrenia and unravelling the differential role of different antipsychotic drugs requires prospective research. (Dinan, 2004) Drug-naïve first-episode schizophrenic patients in Dublin have greater visceral obesity and impaired fasting glucose levels relative to healthy controls. (Thakore et al, 2002; Ryan et al, 2003) Unidentified risk factors for cardiovascular disease and type II diabetes are common in Dublin patients with schizophrenia or schizoaffective disorder. (Behan et al, 2008) A Canadian comparison of schizophrenia subjects and appendicitis controls (Callaghan et al, 2009) reported a significantly increased risk in the former group of being admitted for a cardiac event during 4-year follow-up. Saarni et al (2009), in a Finnish study, found that people with schizophrenia had an excess of abdominal obesity, high fat percentage, and low muscle mass. These were not completely explained by medication, education, diet and smoking. Venkatasubramanian et al (2007) found raised mean plasma insulin and mean insulin resistance score as well as low plasma insulin-like growth factor-1 (IGF-1) in antipsychotic-naïve schizophrenia in India relative to healthy controls. Fernandez-Egea et al (2009) looked at the metabolic profile of antipsychotic-naïve individuals with non-affective psychosis and found significant increases in 2-hour glucose (oral GTT) and IL-6 concentrations.

Spanish¹¹⁷⁶ study of patients with schizophrenia (Bernardo et al, 2009)

National, cross-sectional of patients on second-generation antipsychotics in short-stay units

733 consecutive admissions

Smokers – 71%

Hypercholesterolemia – 66%

Raised triglycerides – 26%

Hypertension – 18%

Diabetes – 5%

Metabolic syndrome – 19-24% depending on definition used

Patients were at increased risk of fatal cardiovascular events

Deduction: cardiovascular risk factors are underdiagnosed and therefore insufficiently treated

It is not yet possible to be definite about the differential risk for different forms of cancer in schizophrenia.

Other conditions

Brief psychotic disorder (DSM-IV; acute and transient psychotic disorder in ICD-10). Considered to be uncommon¹¹⁷⁷, similar patients have been diagnosed as having reactive (brief reactive psychosis in DSM-IV-TR), acute transient polymorphic¹¹⁷⁸, hysterical, psychogenic, or stress-related psychosis, or *bouffée délirante*¹¹⁷⁹ (see below). Jaspers' writings about reactive psychosis describe massive stressors¹¹⁸⁰, a relationship in time between stress and psychosis, a benign course, content of psychosis often reflecting the nature of traumatic experience, and the possibility that psychosis acts as an escape route. DSM-IV stresses a return to premorbid functional level (although recurrences occur in some cases). Stressors may be positive (e.g. promotion) or negative (e.g. being fired), and onset may be postpartum. Good prognosis is associated with high premorbid functioning, few premorbid schizoid traits, severe precipitating stressors, sudden onset, affective symptoms, confusion and perplexity, little affective blunting, short duration, and no schizophrenic relatives.

¹¹⁷⁶ This was conducted in an area with a low cardiovascular disease risk.

¹¹⁷⁷ However, certain groups may be particularly vulnerable, e.g. refugees, military recruits, immigrants, and people exposed to environmental disasters.

¹¹⁷⁸ Research findings conducted using these various labels are difficult to integrate into the general corpus of knowledge, e.g. the possibility of low plasma serine levels in acute transient polymorphic psychosis. (Marneros & Pillman, 2007, p. 108) The reader is referred to Linden et al (2010) who demonstrated a rise in admissions for brief polymorphic psychoses in North Wales during a religious revival (and its attendant intense religious experience) in the first decade of the 20th century.

¹¹⁷⁹ Marneros and Pillman (2007, p. 98) also list cycloid (associated with Kleist, Leonhard, and Perris), atypical (Mitsuda), and non-affective acute remitting (Susser) psychoses. Cycloid psychosis appears as acute polymorphic psychotic disorder in ICD-10, but is not included in DSM-IV.

¹¹⁸⁰ Most cases of brief and acute psychosis do not in fact experience significant life events. (Marneros and Pillman, 2007, p. 110) *Bouffée délirante* is reported from Haiti and West Africa. Sudden onset of agitation, aggression, excitement, and confusion characterise his condition. Some sufferers experience hallucinations and paranoid ideas.

Differential diagnosis includes transient psychosis in personality disordered individuals (particularly, but not confined to, borderline personalities¹¹⁸¹ – especially following stress, often interpersonal), psychosis due to substance use/withdrawal, and psychosis secondary to a medical disorder. Management usually involves admission to hospital since patients are usually floridly psychotic. Response to antipsychotics is often rapid. Continued treatment may be needed in recurrent cases (or in those cases that persist beyond this diagnostic compartment). Patients need psychotherapeutic help to make sense of their experience.

Acute delusional psychosis (*Bouffée délirante*)

Historically associated with Magnan and Ey

Elements of trance or dream state

Acute onset and sudden recovery

Relapse is common

Clouding of consciousness may be present

Intense but fleeting delusions and disturbance of affect

IV sodium amytal makes it worse

Some cases appear to be precipitated by tiredness, infection or other stress

Closely resembles DSM brief psychotic disorder or schizophreniform disorder

Many, perhaps 40%, develop schizophrenia later (?)

Psychiatrists see a large number of acute undifferentiated psychoses resembling everything and fitting nothing - this classification problem is highlighted in our interactions with Third World psychiatrists

Reactive (hysterical, psychogenic) psychosis

Popular in Scandinavia

Person under stress becomes psychotic

Obvious precipitant - onset closely related in time to precipitant

Content reflects precipitant

Clears up with removal of precipitant

Lasts several hours to one month

Patient perplexed and emotional labile

No other cause found

Resembles DSM's brief psychotic disorder or schizophreniform disorder and ICD's and transient psychotic disorders

Paraphrenia: These cases came on later than schizophrenia, showed less destruction of the personality, and often hallucinated. Many psychiatrists would now view paraphrenia as simply schizophrenia of later onset. Indeed, Brodaty et al (1999) failed to distinguish early v late (> 50 years) schizophrenia on any grounds. It is difficult to interpret MRI reports of hyperintensities in such cases. (see Zanetti et al, 2008) ICD-10 divides what was termed 'late paraphrenia' (Frank Fish called this 'senile schizophrenia' in 1960) between schizophrenia and delusional disorder. This is a controversial diagnosis, (Munro, 1999) being diagnosed if onset is over 60 years of age. Late paraphrenia is associated with a wide range of delusions, usually persecutory or referential, hallucinations (usually auditory), and with no catatonia or inappropriate affect, and very rarely is there any formal thought disorder, all of which might suggest that its inclusion under other diagnoses is unwarranted. (Cf. O'Shea, 1997) It is particularly associated with socially isolated, deaf females who show an excess of soft neurological signs. Some authors see late paraphrenia as a heterogeneous disorder. Others regard it as being genetically related to depressive disorders. In general, paranoid symptoms in the elderly are associated with cognitive impairment and social isolation. Almeida (1998) does not accept that late paraphrenia should have 'disappeared' the way it did and does not believe that the excess of females is simply due to late-onset schizophrenia in women. Almeida sees aetiology in this case as an interaction involving age, female sex, social isolation, hearing (mainly conductive) impairment, subtle brain lesions and cognitive decline. Almeida divides late paraphrenia into functional (many psychiatric symptoms including first rank one, and cognitive deficits confined to the executive sphere) and organic (generalised cognitive decline and an excess of neurological signs) types.

¹¹⁸¹ If such episodes are extremely brief (< 1 day) DSM-IV TR categorises them as 'psychiatric disorder not otherwise classified'. However, if they last for > 1 day but < 1 month they are diagnosed as brief psychotic disorder + (whatever) personality disorder.

Frégoli's 'illusion' or delusion, described by Courbon and Fail in 1927 and called after an actor (Léopoldo Frégoli) who was a master of disguise, is different from the Capgras phenomenon (the latter is also called *illusion de sosies* or illusion of doubles). The patient sees a single persecutor, who usually 'follows' the patient about the place, as having many disguises, i.e. he believes a number of people are in fact the one person. The imagined persecutor changes faces or disguises to avoid detection. Both the Capgras and Frégoli phenomena are actually delusions and not illusions, the latter term being misused in this case.

Zombi phenomenon: A Zombi is a person who is raised in a comatose trance from the grave and forced to toil as a slave. Alternative explanations have included the use of potions by the Haitian voodoo priests (tetrodotoxins - potent neurotoxins from certain species of puffer fish) and neurosyphilis.

Dysmorphophobia (body dysmorphic disorder) is discussed elsewhere. However, it should be noted that it can be very difficult to decide if a patient is actually deluded in such cases, the intensity of belief varying between patients and in the same patient. Patients are sure that other people react in a negative way to their appearance and often have ideas or delusions of reference. Extreme cases become housebound because of social avoidance behaviour. Even 'delusional' cases may respond to SSRIs. Both body dysmorphic disorder and OCD may be aggravated by m-chlorophenylpiperazine, a partial 5-HT agonist.

Black Patch Psychosis

Occurs when perceptual deprivation is severe e.g. patient with bilateral corneal transplants forced to lie on his back for a long period of time

Visual and auditory hallucinosis may occur

Uncommon postoperative delirium

Possession states¹¹⁸²

Belief that one is possessed by spirit or ghost

Normal in people with strong cultural beliefs

Delusions of possession are known to occur in depression, schizophrenia, and substance-induced psychoses

Malingering and 'hysteria' are other possible causes

Delusions of bromosis

Belief that one emits an offensive odour

Mainly in young men

Frequent washing and change of clothes frequently

Use strong perfumes and deodorants

May be associated with depression, schizophrenia or TLE, or may conform to the definition of delusional disorder

Ganser's syndrome (Tyndel, 1956)¹¹⁸³

Common in prisoners?

Acute onset

Resolves suddenly

Amnesia for the episode

Must be distinguished from both aphasia and acalculia

Individual symptoms common in other disorders

May follow head injury

Ganser believed it to be a hysterical pseudodementia

Approximate answers¹¹⁸⁴ (*vorbeireden* – Question: 'How many legs has a cow?' Answer: 'Five' or 'three')

Approximate answers have been recorded in association with organic brain disease, intellectual disability and malingering), somatic conversion symptoms (e.g. paresis), visual and/or auditory hallucinations, and clouding of consciousness

¹¹⁸² The author had a patient with borderline personality disorder who believes she is possessed by a demon. Her belief was refractory to medication but abated when ignored.

¹¹⁸³ The German psychiatrist Sigbert Josef Maria Ganser (1853-1931) described this exceedingly rare (Dwyer & Reid, 2004) and controversial (Bass et al, 2000) syndrome in 1898.

¹¹⁸⁴ The term **paralogia** (talking past the point) has been used as a synonym for approximate answers. However it also has a wider meaning of illogicality.

Schizoaffective disorder¹¹⁸⁵: DSM-IV-TR requires a continuous period during which active phase schizophrenia symptoms plus depressive, manic, or mixed mood symptoms occur (*said to exclude schizophrenia*) and during the same episode that delusions or hallucinations are present for at least 2 weeks without being accompanied by prominent mood symptoms (*said to exclude psychotic affective state*). In reality, patients differ in the timing, sequence, degree of overlap, and stability of symptomatology. However, *the occasional episode of mixed 'schizophrenic' and affective symptoms in a person with well-established bipolar affective disorder or recurrent unipolar depression should not necessitate a change in overall diagnosis*. Based on morbidity risks for schizophrenia and affective disorders in relatives, schizoaffective patients seem to some to have an independent disorder, whereas others believe that some cases are truly affective, others really schizophrenic. (O'Shea, 1997; Liddle, 2001, p. 201; Laursen et al., 2005) Diagnostic stability over time has been shown to be relatively poor. (Forrester et al., 2001) Prognosis appears to be better than for schizophrenia but worse than for affective disorders. Poor prognosis is associated with mainly psychotic (particularly negative) symptoms, a family history of schizophrenia, poor premorbid functioning, early or insidious onset, a continuous course, and lack of precipitants. First rank symptoms are not related to outcome. At least 10% commit suicide. Comparatively, prognosis disimproves as we progress along the line of major depression, bipolar disorder, and schizoaffective disorder, to schizophrenia. Schizoaffective disorder has tended to be lumped together with schizophrenia or bipolar disorder in research work. (Abrams & Arciniegas, 2007, p. 86) Some genetic studies suggest that certain genes may confer susceptibility across the functional psychosis spectrum, e.g. the DISC 1 gene¹¹⁸⁶ on 1q42 (Hamshere et al., 2005) and Shao and Vawter (2008), looking for shared gene expression alterations in schizophrenia and bipolar disorder found some examples¹¹⁸⁷ of overlap. Schizoaffective disorder patients, but not those with schizophrenia, may be more likely than healthy controls to carry two copies of the most common BDNF haplotype¹¹⁸⁸. (Lencz et al., 2009) ECT and neuroleptics may relieve 'schizodepressive' episodes, whereas neuroleptics or mood stabilisers (e.g. lithium – not all findings agree) may relieve 'schizomaniac' episodes.

Delusional disorder (DSM-IV): This is the modern name for paranoia/paranoid psychosis or state. F22 in ICD-10 includes delusional disorder, other persistent delusional disorder (insufficient symptoms to diagnose schizophrenia or presence of persistent hallucinations) and persistent delusional disorder, unspecified.

Delusional disorder

Relatively rare (US prevalence = 0.025 to 0.03%; annual incidence of 1 to 3/100,000 population)
 Hallucinations uncommon - tactile and olfactory hallucinations allowed if related to delusional theme
 Can appear normal except when engaged in a topic related to fixed, circumscribed, systematised delusions
 DSM-IV allows non-bizarre¹¹⁸⁹ delusions with content possible in ordinary life, such as being followed or loved from afar
 May be one delusion or a set of related delusions that are usually persistent, if not lifelong; they must be present for at least 3 months
 Delusional content may reflect life experiences
 May act on delusions
 Other symptoms must be a minor or transient finding
 Abnormal eye tracking has been described
 Sex incidence equal or slight female excess
 Usual time of onset is middle age, but earlier onsets are possible (mean = 40 years, range 18 to >90)
 Depressive episodes may occur

Some authors are sceptical about the existence of delusional disorder/paranoia as a separate entity, suggesting that sufficiently lengthy follow up will reveal that many cases will develop schizophrenia. (Sturgeon, 1990) From most to least common, themes of paranoia according to Winokur

¹¹⁸⁵ Such cases resemble Leonhard's 'cycloid psychosis' of the 1950s.

¹¹⁸⁶ Disrupted in schizophrenia 1.

¹¹⁸⁷ 5 dysregulated genes were shared by both disorders and 3 genes (AGXT2L1, SCL1AZ, and TU3A) were highly enriched in brain expression; the differential distribution of AGXT2L1 expression in both disorders vs controls was highly significant ($p < 10^{-06}$).

¹¹⁸⁸ That is the one containing the valine allele of the Val66Met polymorphism.

¹¹⁸⁹ Some delusions are difficult to classify as being bizarre or non-bizarre. (Combs & Mueser, 2007, p. 251)

(1977) include jealous (see Othello syndrome), persecutory, litigious/legal, (Lester ea, 2004) sexual (see erotomania), and scientific (having special knowledge).

Shelton (2008, p. 296) states that two-thirds of cases recover or improve significantly and that one-fifth are chronic and resistant to treatment. However, it is difficult to prognosticate about a disorder that often fails to reach medical attention.

Capgras' syndrome¹¹⁹⁰ (*illusion des sosies*¹¹⁹¹) is present when the patient's spouse, family, friends, pets, furniture or indeed any other possession is believed to have been removed and replaced by an exact double. The double of a loved one may be human, a robot¹¹⁹², or an alien. The fact that one patient believed that her toothbrush was replaced by an identical other is against Sims'(2003, p. 135) contention that replaced objects are emotionally important. Capgras' syndrome may have an organic basis even when it occurs in a setting of a 'functional' disorder (O'Shea, ea, 1989). It has been described in AIDS patients who became confused during an opportunistic infection with an associated right parietal lesion on the CT scan. (Crichton & Lewis, 1990) It has also been described in association with lithium intoxication. The patient may believe that he himself has been replaced by a double (or that a separate double of himself exists), may attack others, develop the syndrome as a child in the setting of shared delusions, or believe that his letters or town has been replaced. It may rarely form part of a transient organic psychosyndrome following ECT. (Hay, 1986) Neuroimaging and neuropsychological research (impaired facial processing) suggest right hemispheric malfunction. (Pull ea, 2003, p. 59) Delusional misidentification syndromes are further discussed in the box. Delusional misidentification was present in 25% of 56 cases of postmortem-verified Alzheimer's disease. (Forstl ea, 1994) Draaisma (2009, p. 283) suggests that Capgras represents a loss of the ability to identify rather than a problem of recognition. He also suggests that there are two face recognition pathways (Draaisma, 2009, p. 295): the conscious (damage leads to *prosopagnosia*: defective face recognition due to occipital damage) and the unconscious/emotional (damage leads to Capgras). However, blind people may develop Capgras delusions and people may believe that loved ones who have emigrated (and therefore cannot be seen) have been replaced! (Draaisma, 2009, p. 297)

Delusional misidentification syndromes (DMSs)

According to Cutting (1991), DMSs involve disturbance in the judgement of identity or uniqueness and the common neuropsychological substrate is right hemisphere dysfunction.

Distortion errors in the perception of others can be divided into (e.g. Ellis, 1997):

- parapsoposia – apparent transformation of a face, usually into a frightening appearance, especially in childhood schizophrenia but also in adults
- intermetamorphosis – appearance of a person's face changes to that of another person
- Frégoli delusion – Q.V.
- Capgras delusion – Q.V.
- subjective doubles – other people have same physical appearance as the patient

Morbid jealousy ('Othello' syndrome¹¹⁹³, 'conjugal paranoia') may be associated with paranoid personality disorder, alcoholism (some cases only reveal themselves when inebriated), cocaine, depression, schizophrenia, brain damage (e.g. pugilists), or early senile dementia. The mechanism probably varies with the underlying cause. Homosexuality does not appear to be of aetiological significance. What is accepted as normal jealousy varies between cultures (e.g. cultures vary in the equality given to female partners) and at different times. Examples of behaviours suggesting morbid jealousy include cross-questioning of partner, using the telephone to ascertain partner's whereabouts, turning up unexpectedly, searching belongings, opening partner's mail, following partner, and examining clothes for evidence of illicit sexual contact. (Mullen & Martin, 1994) Morbid jealousy occurs in both sexes but has been reported more often in men. It may possibly be precipitated or made worse by premenstrual tension. (Mullen & Martin, 1994) Murder of the sexual partner has occurred. Some wives of jealous husbands are housebound because of fear

¹¹⁹⁰ Described by Kahlbaum in 1866, by Clifford Beers (in himself) in 1908, and by the French psychiatrist Jean Marie Joseph Capgras in 1923.

¹¹⁹¹ *Sosies*, a double.

¹¹⁹² One American lady beheaded her stepfather to look for the batteries that she believed would be within! (Blount, 1986)

¹¹⁹³ Although, as pointed out by Munro, (1999) Othello was set up by Iago rather than truly deluded about Desdemona.

of retaliation if they are not always within reach. Affected men are more likely to have symptoms of anxiety and depression, to live alone, to have married very young, and to attempt to ignore perceived threats to their relationship in the hope that it will go away. Affected women are more likely to be jealous if they partake of excess alcohol, to have low self-esteem, to be less than 30 years of age, and to challenge a partner and show overt distress. (Mullen & Martin, 1994) In some cases the jealousy is the chief component of a monosymptomatic delusional state, in which case drugs such as pimozide (Orap) may produce improvement. Crowe (1995) puts forward various approaches that may be useful in managing morbid jealousy. (see box)

Management approaches for morbid jealousy (after Crowe, 1995)

- *Couple therapy* – reciprocity negotiations, communication training, timetables (e.g. discuss problem ideas at set times only), paradoxical injunctions ('I can't cure you. You need jealousy to keep your relationship stable'), reversed role-play (to get other person's perspective across), and sculpting (non-verbal; put each person in positions representing current state of relationship).
- *Individual psychotherapy* – dynamic, cognitive, eclectic.
- *Physical* – antidepressants (SSRIs), antipsychotics.
- *Others* – reduce alcohol intake, separation.
- *Added by Kingham & Gordon (2004)* – treat substance abuse, child protection, hospital admission

Delusions of jealousy are believed, not resisted and are egosyntonic; jealous overvalued ideas are egosyntonic, open to reason, and not resisted; and jealous obsessions are egodystonic, seen as senseless, and usually resisted. (Kingham & Gordon, 2004)

Prognosis depends on underlying phenomenology, comorbidity, and treatment response. Second homicides have been recorded. Careful monitoring over a protracted period is warranted.

Folie à deux¹¹⁹⁴ is a delusion transmitted from one person to another, the couple being emotionally very close. The recipient of the false belief is usually the passive partner and often recovers over a period of months if the two are separated. If three people are involved it is called *folie à trois*, and so on. If the whole family is involved it is styled *folie à famille*. Diagnostic criteria include evidence that the partners have been intimately associated; identical or near identical delusional themes; and acceptance, support and sharing of each other's delusions. The syndrome has been described in 81-year old twin sisters without any evidence of organic brain damage. If one person gets the delusion first and 'infects' another it is called *folie communiquée*. If both develop it together it is called *folie simultanée*. (see box) Separation should be accompanied by help to detach from a dependent relationship. Reuniting such cases (the usual outcome) must be accompanied by regular contact with services. Probably only a minority of these cases resolve on separation only, most cases needing antipsychotic drugs.

Subtypes of 'induced psychosis'

- (a) *Folie imposée*. Induced psychosis. The commonest form (64%). Psychotic, dominant individual induces pseudo-psychosis in recipient, the latter being submissive and suggestible. Recipient does not elaborate on the delusions. Separation may cause the recipient to abandon the delusions.
- (b) *Folie simultanée*. Six percent of cases. Delusions form simultaneously and independently in two people predisposed to develop a true psychosis. Separation does not cause either individual to shed psychopathology.
- (c) *Folie communiquée*. Twenty-five percent of cases. Both individuals are truly psychotic, but onset in one precedes that in the other. The other may take up delusional ideas arising in one of them.
- (d) *Folie induite*. Five percent of cases. A psychotic person may adopt the delusion of another patient and make it his own.

Doppelganger syndrome consists of the delusion of being followed by an exact duplicate of oneself.

¹¹⁹⁴ Described first by Baillarger as *folie à communiquée* in 1860, and then as *folie à deux* by Ernest Charles Lasègue and Jules Falret in 1877.

Erotomania (O'Shea, 2003)¹¹⁹⁵ may be neurotic or psychotic. A female (or less often a male) believes that an unavailable male secretly loves her but is unable to declare this fact. She persecutes him with letters, requests meetings, and so on. Eventually she may turn on him because he does not return her love. It is one cause of stalking. (Mullen ea, 1999) Hayes and O'Shea (1985) have described a case of a woman with Type I schizophrenia who looked after a husband with multiple sclerosis and who developed delusions of this type for a priest. Erotomania can occur in a homosexual setting. The underlying disorder may be depressive or schizophrenic. It can occur in association with organic illness, including AIDS. The object of the delusion may change. The delusion may last for many years, wax and wane, or come in episodes. Some experts believe that it can occur in pure form.

The term 'borderline erotomania' (pathological infatuation) refers to a group whose pursuit of others is pathological but who do not claim to be loved in turn. It may be based on a delusion, an overvalued idea, or an obsession. It may be part of a spectrum that merges with the normal.

The 'incubus syndrome' may be a variant of erotomania. It consists of delusions of imposed sexual approaches or sexual intercourse at night by an unseen lover, the 'incubus'.

Delusional parasitosis,¹¹⁹⁶ a monosymptomatic hypochondriacal psychosis, is one of least three syndromes associated with the Swedish physician K A Ekbohm.¹¹⁹⁷ A person falsely believes that they are infested with insects or worms¹¹⁹⁸. This may be dangerous if the patient burns or floods property. Sufferers may complain of feeling insects stinging, biting or crawling. The patient may wash affected parts excessively, use insecticides or caustics (with secondary dermatitis), use needles to extract 'insects', or burn clothes. Skin may be excoriated, broken or scarred. The *matchbox sign* occurs when a person presents with dust in a box that he believes to be 'bugs'. The latter may be collected on adhesive tape. *Folie à deux* is common in such cases. Freyne and Wrigley (1994) described 6 elderly cases and underlying diagnoses: dementia, drug-induced (Sinemet), primary depression, monosymptomatic hypochondriacal psychosis, and hypochondriasis. There may be an associated organic state¹¹⁹⁹. Many different treatments have been reported as effective¹²⁰⁰. Remission rates are probably the same for typical and atypical antipsychotic drugs. (Lepping ea, 2007)

Delusional parasitosis by proxy may occur in children or pets. (Nel ea, 2001)

Diagnosis

Schizophrenia is a diagnosis that entails clear consciousness and the absence of other (drugs, alcohol, dementia etc) possible causes. Psychiatrists are more likely to tell a patient that he has schizophrenia if it is recurrent than if it is a first episode, a stance that most likely refers to an awareness of initial diagnostic instability rather than any conspiracy of silence. (Wild & Petit, 2002)

Differential diagnosis of schizophrenia

Extreme eccentricity/social isolation/sensory deprivation
 Drug-induced disorders: LSD, cannabis, amphetamines, cocaine, and alcohol (including alcoholic hallucinosis)
 Organic cerebral disorders: temporal lobe epilepsy (TLE), infections, Huntington's disease, etc
 Narcolepsy (hallucinations: Haba-Rubio, 2005)
 Paranoid states - delusional disorder (paranoia) and 'paraphrenia'
 Morbid jealousy
Folie à deux
 Affective and schizoaffective disorders
 Obsessional disorder¹²⁰¹

¹¹⁹⁵ Old Maid's Psychosis, de Clerambault's syndrome, *délires passionnels*, or fantasy lover syndrome.

¹¹⁹⁶ Parasitophobia, delusional infestation, Ekbohm's syndrome, acaraphobia.

¹¹⁹⁷ Ekbohm published his account in 1937, but Thirbierge and Perrin had described the syndrome independently during the 1890s.

¹¹⁹⁸ The present author had a deluded African patient who complained of infestation with the Guinea worm.

¹¹⁹⁹ Alzheimer's disease, Huntington's disease, cerebral infarct, syphilis, cocaine- or amphetamine-induced psychosis.

¹²⁰⁰ Antipsychotics, antidepressants, antipellagrous treatment, B12, iron, leucotomy.

¹²⁰¹ Nechmad ea (2003) found that of 50 adolescents with DSM-IV schizophrenia, 13 (26%) met the DSM-IV criteria for OCD. Obsessive-compulsive symptoms were found to be overrepresented in prodromal (for psychosis: 'ultra-high risk') adolescents by Niendam ea. (2008) Comorbid schizophrenia and OCD ('schizo-OCD') may be associated with particularly severe set-shifting difficulties and there may be an excess of tics. (Patel ea, 2010)

Schizoid or schizotypal personality disorder
 Foreign cultures and sub-cultures
 Adolescent adjustment difficulties
 Gaslight phenomenon: spouse or other caretaker stresses partner/charge in order to induce psychosis-like change in order to have then admitted to hospital

Treatment strategies

'(Before phenothiazines) schizophrenic patients hallucinated openly, talking animatedly to non-existent companions, covering from imagined attack, or preparing to fight imaginary enemies. Delusions were common'. (Jones, 1991)

The treatment of schizophrenia is not confined to a prescription. A package of care should be designed to meet individual requirements. The optimal agent and dose of a treatment can vary over time. (Tandon & Nasrallah, 2006)

According to many authors (Falloon ea, 1998; Drake ea, 2000; Verdoux & Cougnard, 2004; Iyer ea, 2008; Jeppesen ea, 2008; White ea, 2009; McGorry ea, 2010; Saravanan ea, 2010¹²⁰²) duration of untreated psychosis (DUP¹²⁰³) is associated with poor premorbid adjustment, severe negative symptoms, poor insight, social isolation and poor coping skills and shorter DUP correlates with improved prognosis. Possible reasons for delayed access to care in rural Egypt include belief in spirit causes, preference for traditional healers, and being female. (El-Adl ea, 2008) Patients in less well off economies tend to have longer DUPs. (Large ea, 2008) Clarke ea (2007) found that 171 patients in Dublin had an average DUP of 18 months (shorter in mania than in schizophrenia). DUP was not associated with age of onset of psychosis but longer DUP was associated with increased social withdrawal. Less negative symptoms, more years spent in education, and shorter DUP predicted better outcome at 4 years in an Irish study of first-episode schizophrenia. (Whitty ea, 2008) Self-harm was common (11.3%) in first episode psychosis between psychosis onset and presentation to services in an English survey. (Harvey ea, 2008) Independent correlates of self-harm were male sex, social class I/II, depression, and a prolonged DUP. Increased insight was also associated with self-harm. Reducing DUP in first-episode schizophrenia ameliorated negative symptoms in a two-year study. (Melle ea, 2008) Dodgson ea (2008) looked at two groups of psychosis patients, one attending a service in Northumberland before the setting up of an early intervention service and the other following initiation of such a service: the latter had less hospital admissions, less total bed days, and better engagement with the service; also, the authors suggested that an early intervention service saves money in the longer term. A Melbourne study (Henry ea, 2010) followed up first-episode psychosis patients who had presented to the Early Psychosis Prevention and Intervention Centre (EPPIC). Median follow-up was 7 years after index admission. There were 723 cases but follow-up information was available for 651 cases. In the last 2 years, 57% of schizophrenia/schizophreniform cases, 54% of schizoaffective cases, 62% of affective psychosis cases, and 68% of patients with other psychosis reported some paid employment. 37-59% of the cohort achieved remission of their symptoms, 31% were in social/vocational recovery, and around one-quarter of cases were in symptomatic remission and in social/vocational recovery. A major problem with this very positive study was the lack of a control group.

Black people in the UK do not appear to have longer treatment delays than White British patients. (Morgan ea, 2006a) It is strongly suggested that early institution of treatment reduces future relapse rates and prevents or limits deterioration (e.g. Loebel ea, 1992; Scully ea, 1997; Drake, 2000; Harrigan ea, 2003; Keshavan ea, 2003; Melle ea, 2004; Addington ea, 2004; Marshall ea, 2005; Perkins ea, 2005; Garety ea, 2006; Clarke ea, 2006) but some studies disagree that DUP has an influence on treatment response. (e.g. Robinson ea, 1999; Ho ea, 2000) An association between DUP and neurocognitive function at baseline has been found by some (Keshavan ea, 2003) but not all researchers. (Rund ea, 2004; Lawoyin ea, 2007) Larsen ea (2004) reported that patients with a stable social course compared with a deteriorating course had a shorter DUP, but Marshall ea, (2005) in a systematic review, found that premorbid adjustment did not

¹²⁰² This study from India found a relatively good 1-year outcome and changes in psychopathology and insight during the first 6 months and DUP predicted outcome.

¹²⁰³ Due to funding restrictions, the Dublin East Treatment and Early Care Team (DETECT)/Wicklow (DELTA) project was launched in 2005/6 as a pilot project. Basically, patients with early symptoms (e.g. ideas of reference or interference with thinking) and signs (e.g. marked social isolation or impaired scholastic functioning) of (any) psychosis (and their families) receive a battery of tests (e.g. SANS) and, where appropriate, CBT and family psychoeducation are offered. (McWilliams, 2006; Foley, 2006)

explain the observed relationship between DUP and outcome. Perkins *et al* (2004) found that earlier antipsychotic treatment improves outcome in first episode schizophrenia, but so did good premorbid functioning. Barnes *et al* (2008) assesses 98 cases of first episode schizophrenia at presentation and after a year had lapsed: longer DUP predicted more severe positive and negative symptoms and poorer social function at one year, and DUP was not significantly associated with cognition. Norman *et al* (2005) concluded that DUP is probably important for predicting remission of positive symptoms over the first year of treatment, but that the evidence concerning neurotoxicity of DUP is inconsistent. The evidence available is entirely correlational and new approaches to research may provide firmer evidence. An association of longer duration of symptoms with poorer outcome is not unique to psychosis in psychiatry. (Kisely *et al*, 2006) Most cases of first-episode schizophrenia (FES) do not receive treatment until months or even years have passed since the first symptoms developed, which may be toxic to the brain. (Waddington *et al*, 1995) Psychosis may take considerable time to become obviously such and needs to be distinguished from normal adolescence. Morgan *et al* (2006b) found that insidious onset and unemployment increased DUP, the opposite applying to having a family who sought help. A high index of suspicion and a readiness to refer early are suggested. Funding of early intervention teams is controversial in a resource-strapped era, (David, 2004) some authors suggesting that monies are diverted thereby from the care of patients with severe and enduring disorders. (See Pelosi & Birchwood, 2003 for debate) Greater involvement at primary care level is needed to make early intervention work and people need to be helped within the community to seek help. (Shiers & Lester, 2004)

Not all authors agree that there is adequate evidence for early intervention in psychotic disorders. Bosanac *et al* (2010) suggest that there may be no beneficial effects in the long term and that rates of transition to psychosis are too low to justify intervention outside of research settings. Cunningham Owens *et al* (2010) looked at the Northwick Park Study of First Episodes data from the DUP viewpoint: bizarre behaviour at admission made the single biggest contribution to outcome and the authors suggest that DUP may reflect characteristics of psychosis rather than any effect of treatment delay. Gafoor *et al* (2010) reported that early intervention in non-affective psychosis gives superior results to those achieved by generic mental health services but that gains achieved tend to be lost when patients are handed back to the generic team, suggesting that improved generic teams might be as good as early intervention teams.

Non-compliance with treatment in schizophrenia

Major problem

Up to 50% of outpatients do not comply with prescribed treatment

Some patients are cognitively compromised, challenging the idea of informed consent

Reasons given by patients for non-compliance: thinking more clearly (subjectively) when psychotic, side effects (acute dystonia and Parkinsonism common in first-episode cases), feeling better, dissatisfaction with treatment, forgetfulness, lack of transport, financial reasons, failure to improve, employment, confusion over medication, and being out of town

Syrup and depot preparations, and possibly¹²⁰⁴ atypical drugs, (Lieberman *et al*, 2003; Haddad, 2008) increase compliance

Patients prescribed depots tend to have less insight than do those on atypical drugs (Mahadun & Marshall, 2008)

Sophisticated testing suggests very few acute voluntarily admitted patients understand need for antipsychotic drugs (Paul & Oyebode, 1999)

Patients outside hospital have only limited knowledge about their depot medications (Goldbeck *et al*, 1999)

Adherence therapy may not be effective, at least in ordinary clinical settings (Gray *et al*, 2006)

Beta-blockers in high dosage were suggested but have not become popular, results being contradictory. (Wahlbeck *et al*, 2000) They interfere with phenothiazine catabolism, which may account for at least some of their alleged therapeutic activity. Classical (typical) neuroleptics are said to be less effective for negative symptoms (e.g. social withdrawal) than are the newer, atypical agents, although excessive

¹²⁰⁴ Valenstein *et al* (2004) examined compliance by checking on the filling of prescriptions among 63,000 people with schizophrenia in the US Veterans Affairs medical system and found widespread non-compliance for both conventional and atypical antipsychotics.

dosing with the earlier drugs may have been partly responsible.¹²⁰⁵ Antipsychotic medication should be continued for at least 6 months in acute cases. Megadosing with neuroleptics was fashionable but more time on more conservative doses may have the desired effect. There is a potential danger of sudden death when excessive doses are employed. Similarly, caution has replaced rapid neuroleptisation because of the potential risks of neurological and cardiac adverse effects; anyway, the efficacy of rapid escalation of doses in order to speed up response has not found support from research. Cigarette smoking stimulates hepatic enzymes, thereby enhancing drug metabolism. Patients who smoke may need higher doses of antipsychotic drug than do non-smokers. Nicotine reduces Parkinsonian side effects, possibly because of nicotine-dependent activation of dopaminergic neurones. One theory states that there may be a primary defect in the CNS nicotinic system in schizophrenia leading to abnormal sensory gating.

There is insufficient evidence to guide clinicians about when or in whom to stop maintenance drug therapy for schizophrenia. (APA, 2002, p. 433) If a trial off drugs seems warranted dosage should be tapered slowly as this approach is associated with lower relapse rates than is abrupt cessation of medication. McEvoy *et al.* (2006) found clozapine superior to other atypicals in chronic schizophrenic patients who did not respond to one atypical and the same group (Stroup *et al.*, 2006) found that in chronic schizophrenic patients who just stopped taking an atypical that risperidone and olanzapine were more effective than quetiapine and ziprasidone. Use of medication only when symptoms emerge is associated with an increased risk of relapse and admission to hospital. (Schooler *et al.*, 1997) Anyway, so-called early warning signs have only a predictive value of 43%, no better than by chance. (Gaebel, 1999) Benzodiazepines (BZDs) may sometimes prevent progression if given early in the course of a relapse. There is a tendency for schizophrenic patients to receive long term BZDs in conjunction with antipsychotic drugs. The addition of the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib to risperidone improved symptomatology in schizophrenia in a prospective, double-blind study. (Müller *et al.*, 2002) Whether this resulted from an immune action or an NMDA receptor effect was unknown.

In the Robinson *et al.* (1999) study, poor response to antipsychotic medication in first episode schizophrenia or schizoaffective disorder was associated with being male, having a history of OCs, severe hallucinations or delusions, poorer baseline attention, and Parkinsonism during treatment. Whilst Irish GPs usually refer first episode cases of schizophrenia they may avoid prescribing antipsychotic drugs themselves and may advise such patients to continue medication for less than a year. (Gavin *et al.*, 2006)

Sikich *et al.* (2008), using a double-blind methodology, treated paediatric cases of schizophrenia or schizoaffective disorder for 8 weeks with one of three antipsychotic drugs: molindone¹²⁰⁶ showed a 50% response rate plus an excess of akathisia; olanzapine showed a 34% response rate plus an excess of weight increase and metabolic problems; and risperidone showed a 46% response rate plus an excess of weight increase and was associated with weight gain, albeit less than with olanzapine. Aripiprazole was superior to placebo in the acute treatment of 13-17 year-olds with schizophrenia (Findling *et al.*, 2008), the main adverse effects being EPS, somnolence, and tremor.

Strous *et al.* (2003) augmented the antipsychotic therapy of DSM-IV schizophrenics with oral dehydroepiandrosterone (DHEA)¹²⁰⁷ in a double-blind study and found an improvement in negative, depressive, and anxiety symptoms.

Silver *et al.* (2003) and Bodkin *et al.* (2005) found fluvoxamine and selegiline (MAO-B inhibitor) to improve negative symptoms respectively.

Electroconvulsive therapy is still a useful treatment for some cases of schizophrenia. (Chanpattana & Andrade, 2006) Transcranial magnetic stimulation (TMS) applied to the left temporo-parietal region may have beneficial effects on auditory hallucinations. (e.g. Hoffman *et al.*, 1998) However, despite observed improvement in negative symptoms and a trend toward improvement in depression with high-frequency rTMS, Hajak *et al.* (2004) reported a trend for worsening positive symptoms in schizophrenic subjects. Holi *et al.* (2004)¹²⁰⁸ found no therapeutic benefit from rTMS in a group of chronic and severely ill schizophrenia

¹²⁰⁵ **Efficacy v side-effects:** Ganguli and Strassnig (2006) hold that efficacy differences between older and newer drugs (excepting clozapine) are small, that side-effect differences come down to a trade-off (neurological v metabolic), and that the older ones are a cheaper option (especially when treatment is for the long term). The meta-analysis of Crossley *et al.* (2010) found that typical and atypical drugs were of similar efficacy but the side-effect profile was different.

¹²⁰⁶ Patients received benzotropine with this first-generation of antipsychotic.

¹²⁰⁷ Starting with 25 mg/day and titrating up to 100 mg in divided doses during 6 weeks.

¹²⁰⁸ Sham v real rTMS.

patients. Loo ea (2010) found no reduction in auditory hallucinations in subjects with schizophrenia given rTMS during the initial (double-blind, sham-controlled, left and right temporal lobe rTMS) phase of their study but there was a modest improvement during the continuation (open label) phase of treatment. There is a suggestion of abnormal corpus callosum function from TMS research as suggested by a delay in transcortical inhibition. The work of Daskalakis ea (2002) with TMS suggests that schizophrenia is associated with deficits in cortical inhibition and that antipsychotic drugs may increase cortical inhibition.

Management of clozapine-resistance (Williams ea, 2002; Kerwin and Bolonna, 2005)

Consider a longer trial of clozapine¹²⁰⁹

Consider measuring clozapine levels

Adding (or switching to) sulpiride (Shiloh ea, 1997), risperidone (Josiassen ea, 2005¹²¹⁰), aripiprazole (Henderson ea, 2006), pimozide, olanzapine, quetiapine, or lamotrigine

Effect of ECT may not be sustained - continuation/maintenance ECT may be an option (see Hustig & Onilov, 2009)

Psychosocial issues may require attention, e.g. EE, family therapy, compliance therapy, and psychotherapy for hopelessness

Obsessive-compulsive symptoms, common in schizophrenia, may respond to the addition of clomipramine or SSRIs, and fluoxetine may reduce a tendency towards violence, participation in programmes and socialisation in some cases.

Obsessive-compulsive symptoms (OCS) in schizophrenia (Tiryaki & Özkorumak, 2010)

N = 62 patients and 35.5% of these had OCS

Those with OCS had more severe psychotic symptoms and worse quality of life but neurocognitive function was the same whether OCS was present or absent

Positive correlation found between obsessions and delusions and between compulsions and total Scale for the Assessment of Positive Symptoms score and bizarre behaviour subscore

Psychotherapeutic interventions¹²¹¹, practical advice and help with environmental problems, and stress management training (for patients and carers) are helpful. Psychoanalytic treatments are rarely indicated.¹²¹² Psychotic transference phenomena may complicate such approaches, e.g. the patient believes the therapist to be a hostile father and cannot distinguish an as-if feeling from reality. However, psychoanalytic theory may provide useful insights into the meaning of psychotic behaviour and thinking that, when used judiciously, may be helpful.

Cognitive behaviour therapy: In the setting of a non-confrontational, trusting relationship, patients are asked to review symptoms and associated reasoning, to monitor them, to change the focus of attention and to relax, and to modify behaviour.

Cognitive behaviour therapy (CBT)¹²¹³

Not always available (Kingdon, 2006)

Normally an adjunct to medication (Scott, 2007)

Pharmacological stabilisation is a prerequisite before using CBT¹²¹⁴ (Friedman ea, 2008, p. 1935)

¹²⁰⁹ 30% of treatment-resistant patients responded to clozapine and 4% responded to a conventional neuroleptic but when trials lasted at least six months 60% of patients responded to clozapine. (Kane ea, 2001)

¹²¹⁰ But Honer ea (2006) found no advantage with this combination.

¹²¹¹ Most often supportive.

¹²¹² But see Cullberg (2006): whilst one would not employ full psychoanalysis, some cases benefit from limited-goal psychoanalytic-informed help.

¹²¹³ Holloway (2001, p. 173) points out that prioritisation of clinical activities is essential: '... it is futile to demand' **CBT for psychosis** 'if these skills are not available locally'. Various CBT techniques are employed. (see Turkington ea, 2006) The therapist may need to appear neutral regarding delusional beliefs. A strong therapeutic alliance is important. 'Peripheral questioning' is a way of getting the patient to go into details about delusions. 'Inference chaining' involves discovery of the meaning for the patient and the trail of thinking underlying such beliefs. 'Graded reality testing' is the process whereby the patient is brought to question delusions and to consider other possible explanations.

¹²¹⁴ This applies to a number of disorders, e.g. schizophrenia, psychotic depression, and bipolar disorder.

May help patients cope with delusions¹²¹⁵

Startup ea (2004, 2005) reported sustained symptomatic and social functioning benefits in consecutive admissions with acute schizophrenia spectrum disorders who received CBT (v treatment as usual)

Lewis ea (2002) found only transient positive effects for acute symptoms in early schizophrenia

Morrison ea (2004) evaluated efficacy of CBT (given for 6 months) over 12 months in 58 people at very high risk for developing psychosis and found that a reduced likelihood of developing psychosis

Tarrier and Wykes (2004) found no study that showed clear and significant overall differences between CBT and non-specific control groups

Jackson ea (2005) found no advantage for cognitively-orientated psychotherapy over and above routine care for early psychosis

Wykes ea (2005) found that group CBT significantly ameliorated hallucinations only if led by skilled therapists

Jackson ea (2008) found that CBT (up to 20 sessions in 14 weeks) was better than befriending¹²¹⁶ in promoting better early recovery in first-episode psychosis, although the sample was relatively small

In an open trial design (n = 20 adults) 11-weeks of exposure-based CBT reduced PTSD symptoms in patients with PTSD and schizophrenia or schizoaffective disorder and this effect was maintained at 3-month follow-up (Frueh ea, 2009)

CBT may be useful for patients in the early stages of psychosis with problems in the area of social recovery (Fowler ea, 2009)

Meta-analysis: CBT is no better than non-specific control interventions in the treatment of schizophrenia and does not reduce relapse rates (Lynch ea, 2010)

Schizophrenia is over represented among the homeless, many of whom will have no or only erratic contact with mental health services.(O'Shea, 1998) Patients need help to become more active and less withdrawn. Redevelopment of skills can be aided by industrial and occupational therapy, social therapies, living-skills courses, day care programmes, rehabilitation schemes, community care schemes, and sheltered accommodation that provides support and supervision. Halfway houses and hostels may ease transition from hospital to community. Employment at some level, often below their previous level, is essential, be this open or sheltered. The aim of rehabilitation is to promote optimal functioning. Too much or too little pressure should be avoided. Even with optimal rehabilitation, many patients will require continuing attention and care. Schizophrenic patients may improve in an area specifically chosen for treatment, such as one aspect of memory, without benefit generalising to other aspects of the same function. Improvement in verbal memory may correlate with increased task-related activation of the left inferior frontal cortex during fMRI. However, one meta-analysis of cognitive remediation and social skills training in schizophrenia found them to have no benefit (Pilling ea, 2002b) and another meta-analysis (McGurk ea, 2007) found moderate improvement in cognitive performance with cognitive remediation. Krabbendam and Jolles (2002) conclude that the jury is still out on cognitive remediation whereas Szöke ea (2008) suggest that practice produces better results than cognitive remediation. Dickinson ea (2010) found that measures of cognitive function improved with computer-assisted cognitive remediation but that such improvement was not reflected in broader neuropsychological or functional outcome measures. However, Hogarty ea (2004) report positive findings for cognitive enhancement therapy (CET) for stable schizophrenic subjects in a 2-year randomised trial and the positive effects are durable at 1-year follow-up in early schizophrenia.(Eack ea, 2010) Also, there is evidence that cognitive enhancement therapy¹²¹⁷ may increase serum BDNF levels.(Vinogradov ea, 2009a) Cognitive enhancement therapy may also help to preserve grey matter in early schizophrenia.(Eack ea, 2010) Attention shaping, a reward-based learning procedure, may improve attentiveness and promote skill acquisition in people with chronic schizophrenia.(Silverstein ea, 2009) The family and self-help groups need support.(O'Shea, 1994)

Some notes on rehabilitation in schizophrenia

¹²¹⁵ Some of the research evidence for the efficacy suffers from small numbers,(Valmaggia ea, 2005) from non-blindness, and from lack of supervision of drug therapy.

¹²¹⁶ Befriending consists of talking about non-upsetting subjects or engaging in activities such as board games or walking.

¹²¹⁷ Clinically stable, chronic schizophrenia patients received either 50 hours over 10 weeks of computerised auditory and verbal processing training or (with no effect on BDNF levels) computer games.

No medication corrects years of psychosocial damage
 New emphasis on teaching and training with focus on behaviour and functioning – focus less on unfocused industrial-type work and more on specific problem areas
 Treatment planning should be individualised: needs and capacities
 Greater involvement of client in setting goals and planning treatment (may take a long time)
 Impaired information processing is a major obstacle
 Multiple domains involved: attention, abstract reasoning, verbal and working memory, processing speed, sensorimotor integration – determine extra mural performance and ability to stay in social skills program
 Verbal learning is an important predictor of change in performance of daily living skills (Kurtz ea, 2008)
 Difficulty generalising skills from training to real life
Social skills training: small groups; break down behaviours into components; instruct how to master each part; rehearse in simulated social situations – combined with assertive outreach such skills may survive into real life (Lieberman ea, 2001)
Cognitive rehabilitation – e.g. cognitive remediation therapy (Wykes ea, 1999, 2007): one patient to one therapist; graduated focus on executive functioning/problem-solving
Cognitive adaptation training: Environment structured to reduce demands on client, e.g. organising appropriate clothing, reminders re medication, notes on mirrors (Velligan ea, 2000)
Vocational rehabilitation: Case manager finds patient a real job and supports him/her in that position (Drake ea, 1999)

Counselling, help and practical guidance are the main ingredients of such intervention.(see box) A number of families need to be treated to produce a measurable affect on relapse or hospitalisation rates. Treatment needs to be intense and prolonged.(Birchwood & Spencer, 1999) A number of authors have speculated that the main effect of family interventions may be improved medication adherence although Girón ea (2010) found family intervention effects to be independent of compliance and prognostic factors. Others have suggested that when the high dropout rate from family interventions is taken into account (intention to treat analysis) there is a significant reduction in benefit in terms of relapse prevention. Still others have commented on the lack of effect of behavioural interventions on intrafamilial communications. Priority families for intervention include those with a treatment-compliant schizophrenic relative living with them but who relapses frequently, those in whom disagreements erupt into violence, families who resort to the police, and those making heavy demands on staff.

Assertive community treatment (ACT) programmes involve outreach¹²¹⁸, high staffing levels, heavy involvement of nurses and counsellors, frequent visits, direct compliance monitoring, co-ordination of social services by treatment team and careful following of patient through the system, and the use of patient and family satisfaction as outcome measures. The Danish OPUS Trial (Bertelsen ea, 2008) found that such intensive treatment¹²¹⁹ (versus community mental health centres) of first episode psychosis patients improved clinical outcomes at two years but that that the effects were not sustained at five years¹²²⁰.

Family intervention strategies (Kane and McGlashan, 1995)

- *Psychoeducation* – didactic information about the illness; information about vulnerability to relapse/role of stress; understand need for treatment to control symptoms*
- *Stress management* – enhanced communication (listening skills, clarifying wants/needs, providing positive/negative feedback), problem solving (managing daily problems and discrete but significant stressors, general problem solving skills)
- *Crisis intervention* – recognising prodromal signs/symptoms, plans to deal with threatened compliance, active intervention during prodrome or relapse during treatment, and more structured psychosocial programmes

*Burns (1999) stated that that psychoeducation adds little where general services are well developed. Haley (2009), who employed telemedicine in Donegal to link up to a program already provided by St John of God services in Dublin, discussed carer education (not well provided for even in US and UK) the main aims of which are improved empathy, provision of knowledge, non-pathologising

¹²¹⁸ The team goes to the patient.

¹²¹⁹ ACT, psychoeducation, and social skills treatment.

¹²²⁰ However ACT patients fared better in terms of numbers in supported housing and days in hospital.

approach with emphasis on improved coping, communication skills (clear instructions and balance between support and expectations), and better problem solving. Carer education can be provided by a range of health professionals.

Prevention of schizophrenia

There are good reasons why primary prevention is currently impossible. (Murray & Castle, 2000) If all cases with a first degree relative could be prevented, it would remove only about one in ten of all cases. Most babies exposed to severe OCs do not develop schizophrenia (although special care is indicated to avoid hypoxia in the birth of a schizophrenic patient's offspring). Early precursors of schizophrenia in childhood are too non-specific and many children who later develop schizophrenia are perfectly normal as children.

Olanzapine reduces the positive symptoms of prodromal psychotic states but induces weight gain. (McGlashan et al, 2006) There is some evidence that antidepressants or CBT given during the prodrome may help to prevent overt psychosis (Fusar-Poli et al, 2007), although methodological issues (e.g. small numbers and bias in prescribing) abound.

Delusions

As for hallucinations, delusions of influence might simply derive from a real difficulty in attributing one's own actions to the self. (Synofzik et al, 2009) Some patients derive meaning and importance from their delusions, recovery being too much to bear. A schizophrenic patient may believe that he is the president of his country whilst residing in gaol for petty theft: this profound lack of awareness of a fundamental contradiction is called *double orientation*.¹²²¹ Psychoanalysts have interpreted delusions as providing a defence against low self-esteem, although it is difficult to see how a delusion of persecution could fulfil this role (unless persecution is equated with self-importance¹²²²). Delusions tend to keep pace with the times, e.g. being spied upon by satellite dishes during the late twentieth century.

Somatic delusions relate to the body. McGilchrist and Cutting (1995) found that male schizophrenics located abnormal phenomena principally on the left with depressives locating them on the opposite side, results that might relate to localisation of brain dysfunction in psychosis. The schizophrenic patients typically had delusions of a 'peculiar' sensation, or, more specifically, of rotation and paraesthesiae. Depressives more often had delusions of blockage, pressure, weight, fullness, liquidity, pain or weakness.

Hallucinations

Perhaps half of psychiatric patients who have auditory vocal hallucinations experience welcome as well as unwelcome voices, and up to half of them wish to keep them. (Jenner et al, 2008) Deaf people can have auditory hallucinations and people blinded by cataracts can experience visual hallucinations. Hallucinations are often said to be experienced as originating in the outside world or within one's own body, but not, according to time-honoured dogma, within the mind as through imagination¹²²³. Third person auditory hallucinations heard in clear consciousness are not unique to schizophrenia, being found also in alcoholic hallucinosis. Auditory hallucinations are common in mania. It is suggested that people that feel marginalised or subordinate in society may hear voices of people they believe to be their superiors. It has been known for many years that direct stimulation of superior temporal gyrus structures can provoke complex hallucinations. Altered preconscious planning of discourse has been suggested as a cause of auditory hallucinations in schizophrenia. Defective feedback so that self-generated subvocal speech is not recognised as such constitutes another such hypothesis. (Stephane et al, 2010) The problem may be in disrupted speech perception and verbal working memory rather than in non-language cognitive or attentional deficits. Imagining sentences spoken in another person's voice necessitates monitoring of inner speech. Using this technique and PET it has been shown that hallucinating schizophrenics deactivate the *left* middle temporal gyrus and the rostral supplementary motor area, these parts of the brain being strongly activated by normals and non-hallucinating schizophrenics. However, an fMRI study (Shergill et al, 2003) found that getting the schizophrenic subject to increase the rate of inner speech was associated with a relatively attenuated response in the *right* temporal, parietal, parahippocampal and cerebellar cortex. Also, Diederer et al (2010), also using fMRI, found that patients with a psychotic disorder deactivated the

¹²²¹ In the past, this same phenomenon was well described in sufferers from general paresis (e.g. Al Capone).

¹²²² However, one sometimes sees a patient with so-called '*delusions of assistance*' wherein persons/deity/forces/powers/organisations try to help him/her improve themselves or overcome some problem. (McKenna, 2007, p. 3)

¹²²³ However, many patients admit that voices are heard inside the head. (Mayer-Gross et al, 1969; Lawrie & Johnstone, 2004, p. 394; McKenna, 2007, p. 197)

parahippocampal gyrus *before* reporting auditory verbal hallucinations. Hoffman *et al.* (2008) performed fMRI on six right-handed (dextral) patients with either DSM-IV schizophrenia or schizo-affective disorder in order to map changes before onset of auditory hallucinations. Patients activated left anterior insula and right middle temporal gyrus and deactivated anterior cingulate and parahippocampal gyri. In another study, when hallucinators imagined speech they differed from other groups by their reduction in activity of the parietal operculum. (McGuire *et al.*, 1996) However, some authors have found no evidence that schizophrenic people are unable to distinguish an inner voice from external speech. Others have found an inability of patients with a wide range of psychoses who had auditory hallucinations or passivity phenomena to distinguish between self-stimulation and external stimulation (tap own palm *v* experimenter doing so). Maruff *et al.* (2005), using MRI, found a connection between reduced volumes of parietal and frontal association areas and motor passivity delusions. Fu *et al.* (2001) got healthy volunteers and schizophrenic patients to read adjectives aloud, their voice then been audible in a distorted or undistorted manner. Controls hearing their own distorted voice activated hippocampus, cingulate and cerebellum. Acutely psychotic patients failed to engage these areas of the brain and tended to attribute their own distorted voice to other people. Remitted patients showed activation patterns intermediate between the controls and the acute psychotics.

Unilateral auditory hallucinations have been reported in association with a contralateral left superior temporal gyrus lesion and ipsilateral conductive deafness; the hallucinations stopped on wearing a hearing aid. MRI studies suggest that schizophrenics with auditory hallucinations have a smaller superior temporal gyrus. (O'Shea, 1997) PET studies in hallucinating schizophrenic patients suggest low metabolism in the right hemisphere homologue of Broca's area; severity of hallucinations are related to relative metabolism in striatal and anterior cingulate areas; and antipsychotic drugs increase striatal metabolism. (Cleghorn *et al.*, 1992) SPECT studies reveal increased blood flow in Broca's area under the same circumstances. (McGuire *et al.*, 1993) In the Shergill *et al.* (2000) study, fMRI revealed evidence for attenuated activation when schizophrenic patients with auditory hallucinations were processing inner speech in areas implicated in verbal self-monitoring (posterior cerebellar cortex, hippocampi, superior temporal cortex, and nucleus accumbens). Other fMRI work suggests involvement of somewhat different areas. Probably, auditory hallucinations involve a number of cortical and subcortical areas.

Visual hallucinations are probably much more common in chronic schizophrenia than we generally think. According to Dubovsky and Thomas (1992) visual and auditory hallucinations are equally common in psychotic depression. Visual hallucinations¹²²⁴ are common in Lewy body dementia and have been reported in a minority of dissociative (hysterical) cases. Hallucinations as conversion symptoms ('pseudohallucinations') have a long history and *may* differ in a number of ways from those seen in the psychoses, e.g. childish content (e.g. a giant pink panda), personal meaning (e.g. wish fulfilment), a subjective sense that the hallucinations are not true, multiple-modality involvement, and absence of other manifestations of psychosis. DSM-IV-TR mandates that dissociative identity disorder and PTSD be outruled before diagnosing hallucinations as conversion symptoms. Hallucinations associated with bereavement should also be kept in mind.

The *Charles Bonnet syndrome* consists of poor sight and visual hallucinations.

Autoscopic hallucinations are visual hallucinations of all or part of the self. The vision is usually transparent and colourless and imitates the patient's movements. Onset is usually sudden, unheralded, as with a phantom. Most cases do not progress or incapacitate, the person being able to remain emotionally detached from the experience. An underlying brain lesion should be considered. Autoscopic hallucinations are rare in the functional psychoses, including schizophrenia.

Heautoscopy, an extension of autoscopia, refers to the projection of sensation as well as visual aspects of the self – the patient is able to see and feel his double outside the self. This is different from two phenomena that may occur together in some organic disorders: a *feeling of presence* (feeling that an invisible other being is close by) and from *out of body experience* (feeling that one is separated from one's body).

¹²²⁴ Some people with Parkinson's disease experience visual hallucinations that might reflect dopamine disturbance in the visual system or REM sleep breakthrough whilst napping.

Various non-drug therapies of variable efficacy have been advocated for auditory hallucinations, such as unilateral earplugs (rarely effective), subvocal counting or singing, and listening to music through headphones.

Synaesthesia (stimulation of one sensory modality is experienced as an hallucination in another modality, e.g. 'seeing music') is classically associated with LSD₂₅, although they can occur in people with normal mental states as when a cold feeling in the back follows scraping of a finger nail on a blackboard.

Splitting of perception, a rare experience found in schizophrenia or organic disorders, involves a failure to make the normal link between two or more perceptions, as when a patient watching a movie experiences the visual and sound elements to arise from unconnected sources¹²²⁵.

Musical hallucinations

The composer Schumann believed that deceased composers were dictating melodies that he could hear. Risk factors include acquired deafness, being female or old, cerebral pathology, and being isolated from other people. They have been reported in a number of disorders (e.g. schizophrenia, depression, dementia, salicylates, benzodiazepines, propranolol, clomipramine, ECT, and chronic alcoholism) but may be an isolated non-psychotic phenomenon. The superior temporal lobe may be involved as shown by neuroimaging studies; neurological lesions (tumour, CVA, epileptic focus) may be more common on the right than the left; there may be a history of tinnitus.(see Stewart ea, 2006) Bilateral musical hallucinations were described in a syphilitic woman in Wakefield asylum with brain damage associated with focal epilepsy following surgery during the 1890s. Her mental state is said to have improved despite these complications!(Goodall, 1893) Musical hallucinations were elicited at surgery during the 1950s by stimulating the temporal cortex. They may occur in association with vascular lesions of the left temporal/parietal lobes. Some musical hallucinations may respond to anticonvulsants and be refractory to antipsychotic drugs.

In *phantom radio* the patient hears repetitive instrumental or vocal music, often familiar to the patient.(Warner & Aziz, 2005)

Command hallucinations (e.g. 'Assault her!') should alert carers to the possibility of violence to the self or others.

People who value their hallucinations before receiving treatment are more likely than others to be hallucinating despite being treated. Chronic hallucinations may be viewed as 'companions' or as 'persecutors'. The number of reported 'voices' may increase, dialogue may become extended, and the degree of intimacy with the subject may also increase.(Nayani & David, 1996) Even if treatment does not rid the patient of hallucinations they may become less frequent or intense and less likely to determine overt behaviour.(Miller, 1996)

Catatonia

Once commonly reported,(Kahlbaum, 1874, O'Shea, 2001; Bräunig & Krüger, 2004; Rajagopal, 2007; Fink & Taylor, 2009) catatonia has become apparently 'rare' (or missed) and non-specific,(Caroff ea, 2004) especially in developed countries, at least in its classical form.(Chalasani ea, 2005) Catatonia has been reported to be more common in affective disorders (Dabholkar, 1988; Taylor & Fink, 2003) than in schizophrenia. Hysterical cases are rare. Other causes include brain disease, metabolic disturbances, alcohol and drugs.

¹²²⁵ Badly dubbed movies excluded.



Karl Ludwig Kahlbaum (1828-1899)

*Organic causes of catatonia*¹²²⁶

Infection¹²²⁷
 Head injury
 Cerebral tumours
 Vascular¹²²⁸
 Wenicke's encephalopathy
 Multiple sclerosis
 Lesions of third ventricle, brain stem, or basal ganglia
 Metabolic¹²²⁹
 Drugs¹²³⁰
 Benzodiazepine withdrawal
 Epileptic¹²³¹
 Childhood affectations – learning disability, autism, Prader-Willi syndrome

The EEG is generally normal in catatonia.

Catatonia seems to be a disorder of the appropriate termination of movement rather than of initiation as in Parkinson's disease.

Suggested mechanisms underlying catatonia

Neuroimaging studies suggest a mainly *cortical disorder* in catatonia, whereas NMS is a basal ganglia disorder with secondary involvement of cortical motor structures (Northoff, 2004)
 Catatonic withdrawal represents *primitive avoidance-separation behaviour* (Fricchione, 2004)
GABA deficiency (BZDs are used in treatment)
Sudden and massive blockade of DA (antipsychotics may precipitate/exacerbate the disorder)
Cholinergic and serotonergic rebound (as in clozapine-withdrawal catatonia)

Apart from catatonic schizophrenia itself, other schizophrenic subtypes may manifest transient and single catatonic symptoms. Whether it is a subtype of the neuroleptic malignant syndrome (NMS) is debatable (*cf. infra*). According to Carroll, (2001) 10% of catatonic patients may develop NMS. Although more than forty motor signs of catatonia are known, Taylor and Fink (2003) would make the diagnosis if two prominent features were present for at least 24 hours. Using the Taylor and Fink definition, catatonia occurs in about one in ten acute psychiatric inpatients. Studies in rats found that endorphin injected into the cerebral ventricles lead to catatonia. Therefore, it was suggested that intravenous naloxone would reverse catatonia in man. However, there is little evidence to support this contention, including the present author's clinical

¹²²⁶ Organic catatonic disorder in ICD-10, catatonic disorder due to a general medical condition in DSM-IV.

¹²²⁷ E.g. anti-NMDAR encephalitis (a paraneoplastic syndrome with anti-NMDA receptor antibodies), encephalitis lethargica, herpes simplex.

¹²²⁸ Basilar thrombosis.

¹²²⁹ Hyperthyroidism, porphyria, hypercalcaemia, diabetic ketoacidosis, carcinoid syndrome, hepatic encephalopathy, homocystinuria, carbon monoxide, NMS.

¹²³⁰ Alcohol, disulfiram, neuroleptics, lithium, amphetamines, phencyclidine, corticosteroids.

¹²³¹ Non-convulsive epileptic status.

experience. Complex dysfunctions of DA, GABA-A and GABA-B, and NMDA receptors may be involved in catatonia.

ICD-10 criteria for catatonic schizophrenia (F20.2)

Prominent psychomotor disturbances

May alternate between hyperkinesia and stupor, or automatic obedience and negativism

Constrained attitudes and postures may be held for prolonged periods

There may be episodes of violent excitement

Catatonic phenomena may be combined with an oneiroid (dream-like imagery) state¹²³² with vivid scenic hallucinations

Chronic schizophrenic patients may have command automatisms (automatic compliance with instructions) and perseveration of words and phrases.

General features of catatonia

Psychomotor disturbances predominate: can change from stupor to hyperactivity

Waxy flexibility (flexibilitas cerea): found in catatonic schizophrenia (stuporose type) - resistance to passive limb movement resembling that found on bending the candles of yesteryear; *blocking/freezing* refers to the sudden stopping of a purposive movement midway in its enactment, followed by fixation in that position or gradual return to the resting position; waxy flexibility may also occur in hepatic encephalopathy

Maintenance of imposed postures – a limb left in any position will remain there, despite gravity¹²³³

Stereotypy, posturing, catalepsy, echolalia and echopraxia; automatic obedience - unquestioningly does what is requested

Obstruction: intermittent difficulty/inability to carry out an action; may not complete intended actions - may resist compliance until examiner appears to stop requesting an action (despite repeated requests to be seated nothing happens until examiner goes to leave)

Opposition: opposition to attempted passive movement

Negativism:¹²³⁴ apparently motiveless resistance to suggestion or interference (refuses to carry out requests or follow instructions)

'Command negativism': patient reflexly does the opposite of what is asked of him (if asked to approach, he retreats; if asked to keep seated, he stands)

Mutism - no verbal communication¹²³⁵; found with severe depression or catatonic schizophrenia

Mood may be depressive or hypomanic

Psychological pillow: patient may lie in bed with his head just off the pillow, requiring sustained sternocleidomastoid muscle contraction. This may last for hours!¹²³⁶ It is also found in dementia.

Catatonic symptoms are not always easy to distinguish from extrapyramidal side effects of drugs, with which they may be related neuro-anatomically. Amobarbital given intravenously may assist in the interview of a catatonic mute, the response being better in one randomised blind trial (compared with saline) if the patient was older and female.

In psychiatric stupor¹²³⁷, the patient is mute, immobile, and conscious; if the eyes are open the patient may follow external movement; there is resistance to passive eye-opening; and the patient is aware of what is being said. The causes of (psychiatric) stupor include psychogenic (rare), depression, mania, catatonic schizophrenia, and akinetic (organic), e.g. Rathke's pouch tumour, cysts of third ventricle.

Medical complications of chronic catatonia

¹²³² The person is awake. Prolonged oneiroid states are sometimes called twilight states.

¹²³³ *Mitmachen* refers to an extreme form of obedience: therapist able to place patient's body part in any position without being resisted, the part slowly returning to its resting position.

¹²³⁴ Somewhat the same is '*ambitendency*': series of hesitant, incomplete movements when expected to perform a voluntary action, e.g. keeps extending and withdrawing his hand when examiner offers his in greeting.

¹²³⁵ A few mute patients may say something as the psychiatrist takes his/her leave: *reaction of the last moment*. This is different from patients who only reveal the crux of the problem at the end of an interview.

¹²³⁶ Maintenance of an uncomfortable position for a few seconds has been called *Haltungsverharren*.

¹²³⁷ Neurologists use the term to infer a reduced level of consciousness.

Dehydration, malnutrition, constipation/ileus
 Dental caries/gum disease/fungal oral (and vaginal) disease from antibiotics, aspiration leading to pneumonia and/or pneumonia
 Venous stasis/thrombosis/pulmonary embolism
 Decubitus ulceration
 Urinary retention due to bladder distension, urinary incontinence, urinary tract infection (e.g. indwelling catheter)
 Complications of nasogastric/feeding tube usage¹²³⁸
 Pressure nerve palsies, flexion contractures, vaginal infections (poor hygiene), and colonisation by fleas¹²³⁹
 Rhabdomyolysis (due to prolonged immobility) has been reported in acute lethal catatonia, severe neuroleptic-induced dystonia, and NMS (Levenson & Pandurangi, 2004)

Catatonia responds to benzodiazepines (BZDs) and/or electroconvulsive therapy (ECT). If BZDs fail and ECT is subsequently used treatment parameters may need adjustment due to a raised seizure threshold. BZDs may be less effective in catatonic schizophrenia. (Rosebush & Mazurek, 2004) Bromocriptine may ameliorate both NMS and catatonic stupor. In one study, patients with high Abnormal Involuntary Movement Scale (AIMS) scores and low levels of Parkinsonism had high creatine phosphokinase (CPK) levels and a tendency to respond to lorazepam (Ativan); those with low CPK levels, low AIMS scores and high levels of Parkinsonism tended to be lorazepam-resistant. Lorazepam has demonstrated efficacy in prospective studies whereas neuroleptics have low efficacy. (APA, 2002, p. 567) Amantadine (100 mgs. b.i.d. for several weeks) has been suggested for neuroleptic-induced catatonia. Acute catatonia has also been treated with IV amantadine. IM and IV anticholinergic agents have been used effectively in some cases. Sodium amobarbital can also be effective. (Rosebush & Mazurek, 2004) ECT is the first choice in treatment for lethal (malignant) catatonia. (Petrides et al, 2004)

Comorbid medical disorders should be stabilised. Seizure-induced cases may respond to lorazepam and anticonvulsant drugs. Dehydration, nutritional disorders, infection (e.g. pneumonia), bedsores, and deep vein thrombosis with pulmonary embolism (from immobility) should be prevented. (Carroll & Goforth, 2004)

Gjessing's syndrome (periodic catatonia)

Rare disorder of cyclical nitrogen retention (Gjessing, 1938)¹²⁴⁰
 Nitrogen retention causes psychosis
 May not constitute one disorder¹²⁴¹
 Attempts at replicating Gjessing's findings have not been uniformly successful (Minde, 1966)
 Reported as autosomal dominant disorder with disease locus mapping to chromosomes 15q15 and 22q13¹²⁴² in different families (Beld et al, 2004)
 According to Beld et al, (2004) most cases are misdiagnosed and partially treated
 Was managed by giving thyroid hormones or low nitrogen diet to deplete body nitrogen storage – this may have helped some cases - modern pharmacotherapy largely replaced such approaches

Stauder's acute lethal (malignant, pernicious) catatonia: This rare condition¹²⁴³ could cause sudden death in psychiatric patients and was well known before the neuroleptic era.

¹²³⁸ Oesophagitis, pneumothorax, empyema, bronchopleural fistula, diarrhoea, dependent oedema, bacterial contamination of stomach contents, hypoglycaemia, hypercapnia, electrolyte imbalances.

¹²³⁹ One case had moving circular colonies in the finger web spaces.

¹²⁴⁰ Named for Rolf (or Rolv) Gjessing (1889-1959), a Norwegian psychiatrist.

¹²⁴¹ According to McKenna (2007, p. 368) a schizophrenic outcome was 'evident' in Gjessing's cases. Also, these patients do not seem to have been mentally recovered between attacks (apathy, dullness, insightless).

¹²⁴² The affected gene at 22q13 is WKL1. This gene carries the code for a cation channel protein found in dorsal striatum and the limbic system.

¹²⁴³ Stauder published details of 27 cases of 'lethal catatonia' in 1934, although Calmeil, Bell ('Bell's mania'), and Schüle (Schüle's *delirium acutum*) had described the same syndrome in 1832, 1849, and 1867 respectively. (Bräunig & Krüger, 2004; Mann et al, 2004)

Clinical picture

Personality change
 Mood disorder
 Hyperactivity
 Hallucinations
 Delusions
 Confusion
 Catatonia

Often begins with extreme psychotic excitement, which, if persistent, can lead to fever, exhaustion, and death from respiratory arrest or cardiovascular collapse*

*NMS starts with severe extrapyramidal muscle rigidity (less so when atypical drugs, including clozapine, are involved¹²⁴⁴) and necessitates immediate cessation of neuroleptics, which are ineffective in lethal catatonia. It is therefore important to differentiate between them, but catatonia may precede NMS and may be a risk factor for NMS.

There may be a prodrome lasting weeks to months with behavioural and personality changes or frank schizophrenic symptoms. Alternatively, there may be an acute onset without prodrome. Excitement follows, with intense anxiety and restlessness lasting a few days. There may be self-destructive or assaultive behaviour. Sometimes there are fever, tachycardia, and acrocyanosis. The complete syndrome may include choreiform movements, mutism, rigidity, and/or stupor alternating with excitement. There may be an increasing and fluctuating fever, rapid and weak pulse, profuse and clammy perspiration, and hypotension. Towards the end there are cachexia, convulsions, delirium, coma, and exhaustion. Sudden death may terminate the episode.

The relationship between lethal catatonia and NMS is controversial and both disorders may be clinically identical, or, more controversially, possibly both conditions are the same entity. Lethal catatonia may have become even rarer after the 1950s, when neuroleptics became available.

Antipsychotic drugs should be withheld. ECT may be the most effective treatment (Petrides *et al*, 2004), especially if given before the onset of coma. (Sackeim, 2003, p. 535) If benzodiazepines (BZDs) have failed, they should not be withdrawn rapidly (withdrawal may provoke or worsen catatonia). Petrides *et al* (2004) suggest continuing BZDs during ECT. Some patients may need to their BZDs continued for some time after ECT.

There is no laboratory test to help differentiate lethal (malignant) catatonia from NMS. Whilst low serum iron is extremely common in both NMS (96%) and lethal catatonia (100%), it is only found in 34-35% of cases of simple catatonia. (Lee, 2004) Low serum iron is found in many disorders (inflammatory, infectious, tissue destruction, strenuous exercise, and stress). Why iron levels should be depressed in catatonia and NMS is unknown but iron is important for D2 receptor structure and function, perhaps leading to reduced D2 receptor numbers in the basal ganglia. Nevertheless, central and peripheral iron levels are poorly correlated with one another. (Sachdev, 1993) Whilst CPK and leucocyte levels are raised in most cases of NMS and lethal catatonia, leucocytosis is uncommon in simple catatonia and CPK levels are raised in a majority of simple catatonic cases. (Lee, 2004) According to Insel *et al* (2008) low maternal haemoglobin concentration may be a risk factor for 'schizophrenia spectrum disorders' in their offspring¹²⁴⁵.

In conclusion, catatonic features nowadays are most common in affective disorder, especially mania. They are also seen in organic states and, but not pathognomically, in schizophrenia. Catatonia is best viewed as a syndrome rather than a final diagnosis. Subtle forms are often missed or ignored. Classically, for acute or prophylactic management, ECT may be the most effective therapy in most cases, although benzodiazepines (BZDs) are gaining favour. ECT may be combined with BZDs in such cases, and the combination may act synergistically, probably because both approaches increase the seizure threshold.

¹²⁴⁴ CPK levels may be normal in NMS secondary to atypical drugs. (Fricchione *et al*, 2008, p. 767) Also, CPK is often raised in catatonia.

¹²⁴⁵ Does this mean that iron deficiency (iron is important for brain development and function) predisposes to schizophrenia or that mothers carrying children predisposed to schizophrenia are relatively undernourished any way?

Address

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Affective (mood) disorders and suicidology

Brian O'Shea

'We need a paradigm shift to recognise that depression is a life course disorder'. (Scott, 2006)

Affective disorders include conditions characterised by excessive depression (L. *de*, down, *premere*, to press) or elation of mood. Depression may mean an appropriate mood state, a symptom, or an illness.

Cost

Mood disorders represent about 21% of the cost of mental illness in America.

Economics of mood disorders¹²⁴⁶

Global

In 2006 WHO says depression is leading cause of years lost because of disability¹²⁴⁷

Republic of Ireland

Total cost of depression for 1993 = c. £99 million¹²⁴⁸

Economic productivity loss of 280 young adult suicides 1981-94 = c. IR£75,600,000¹²⁴⁹

Europe

Working day loss in previous 30 days due to depression, cardiac disease, and diabetes respectively = 9%, 7%, and 2%¹²⁵⁰

USA

Annual cost of depression 1993 = c. \$43.7 billion¹²⁵¹

Cost of affective disorders 1985 = c. \$20.8 bn, 1990 = c. \$30.4 bn

Annual cost of depression the late 1990s = c. \$15 bn

Canada

Premature mortality and reduced productivity due to depression costs C\$2.53bn¹²⁵² which represents 58% of overall economic cost of depression

UK

Annual cost of depression (UK) late 1990s = £2 bn

Total cost of adult depression in the England during 2000 at £9 bn¹²⁵³

Annual cost (UK) of bipolar disorder = c. £2 bn (1999/2000 prices)¹²⁵⁴

¹²⁴⁶ €1 = IR£0.79 at introduction of euro.

¹²⁴⁷ Reifler (2006)

¹²⁴⁸ Keogh and Walsh (1995)

¹²⁴⁹ National Task Force on Suicide (1998). The National Task Force on Suicide, estab. 1995.

¹²⁵⁰ Wittchen and Jacobi (2005)

¹²⁵¹ 28% direct costs, 17% mortality costs, and 55% derived from morbidity cost categories, i.e. absenteeism and reduced productivity.

¹²⁵² (Lam & Mok, 2008, p. 7)

¹²⁵³ Thomas and Morris (2003): £370,000,000 direct treatment costs; 109.7 million working days lost; 2,615 deaths.

¹²⁵⁴ Gupta and Guest(2002): 86% = indirect costs.

As a generalisation, indirect costs (e.g. productivity loss) are about seven times direct (e.g. medication) costs. Direct costs of treating major depressive disorder (MDD) with antidepressants among US employees increased if there was a comorbid anxiety disorder. (Birnbaum *et al*, 2009)

TCAs are cheaper as far as direct costs are concerned than SSRIs as first-line treatments, although complex calculations have been published arguing that SSRIs may be cheaper in the long run when total costs (including side effect burden and ICU care after overdose) is included. One argument against the finding that SSRIs are ultimately cheaper than TCAs is that if economic outcome studies were long enough (> 1 year) TCAs would come out cheaper. (Woods & Baker, 1999) Baker *et al* (2003) conclude that 'pharmacoeconomic studies of antidepressants reveal clear associations of study sponsorship with quantitative outcome'! Many authors reserve TCAs for depression (especially 'melancholia') resistant to other drugs. (Howland & Thase, 2002) Chisholm *et al* (2004) state that older antidepressants are more cost-effective than the newer drugs, particularly in poorer parts of the world.

*Epidemiology*¹²⁵⁵

'With the exception of hypertension depression is likely to be the commonest condition seen in primary care'. (Tylee & Walters, 2002)

In the early 1970s, between 3-4% of the general population were found to be depressed at any one time (point prevalence). One in five sought medical advice from a GP or specialist, one in fifty were hospitalised, and one in two hundred committed suicide. About one in twenty had a future manic episode. Most would have a further attack of depression. Major depression has a point prevalence of about 5% in the general population. Depressive illness, like suicide, is most common in spring and autumn (Postolache *et al*, 2009), although the reasons for this remain unknown. Whilst women present more often than men with depression, there is some evidence that this gap between the sexes may not be as wide as heretofore because of changing social roles. Scott (1988) reviewed the subject of chronic depression and, when defined as persistent symptoms of depression for two or more years, gave it a prevalence of 2-15%. It has been suggested that most cases of depression treated in general practice satisfied criteria (e.g. PSE or RDC) for psychiatric disorder but tended to be relatively mild and borderline in quality. They were said to be much less severely ill than outpatients, have less depressive symptoms and a shorter illness, and less primary and less endogenous depression. However, while severe, suicidal and psychotic depression can be expected to cluster in in-patient settings, major depression may not differ much between GP and psychiatric OPD settings. (Vuorilehto *et al*, 2007) Barrett *et al* (1988) estimated an 11-36% frequency of diagnosable psychiatric disorders in general practice (GP).

McGuffin and Katz (1986)

Morbid risk of bipolar illness (BP) in first degree relatives of BP probands = 8% and of unipolar illness (UP) = 11%

Morbid risk is for UP illness only among relatives of UP probands (9%)

Reich *et al* (1982)

Lifetime risk in general population for BP and UP disorder = <1% (figures vary: 0.5-15%) and 3% respectively

Andreasen *et al* (1987)

1.1% of relatives of BP II probands have BP I illness

8.2% of relatives of BP II probands have BP II illness

Kennedy *et al* (2005)

35-year epidemiological study of BP

74% of 246 first episode mania cases experienced psychotic symptoms

A BP parent is more likely to have a UP than a BP offspring, but is most likely to have a child who will develop neither. (Kay & Tasman, 2006, p. 557) Other examples of published statistics are given in the table.

Summarised epidemiology of affective disorders¹²⁵⁶

¹²⁵⁵ See Parker and Hickie (2007) for a debate on whether depression is over- or under-diagnosed. Tyrer and Silk (2008, p. 13) suggest that as the number of people receiving antidepressant drugs increase the threshold for prescribing such drugs has been lowered.

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<i>Year</i>	<i>Findings</i>	<i>Comments</i>
1939 & 1956	BP found throughout cities	Schizophrenia in city centres
1988	Major depression LP = 5%	USA
1988	Dysthymia LP = 3%	ECA (F>M) ¹²⁵⁷
1992	Prevalence of Depression in GH = 5.2%	Standardised interview (UK)
1992	Major depression LP = 16%	Zurich
1994	Major depression LP = 17%	USA
1995	Autumn preponderance of depression and no specific seasonality for mania	London and Dunedin, NZ
1995	90% of cases of mania have BP relapse	
1995	Psychosis in MDD increases likelihood of BP Type I disorder diagnosis	
1997	Suicide prevalence 9-10/100,000	UK; especially young M, middle-aged F; mostly overdose, violent in 30%; highest in April-June
1999	7.9% of years lived with disability from depression in Australia	Dementia was next (5.6%), then asthma (4.8%)
2000	9.4% of years lived with disability from depression worldwide	Adult deafness was next (5.5%), then cataracts (5.2%)
2000	Failed to find seasonality for suicide	UK
2002	Study of 15 primary care centres: 15-fold variation in prevalence of current major depression: high prevalence associated with lower impairment	14 countries; raises question of definition
2002	17% and 10% of Irish psychiatric inpatients had diagnoses of depression and mania respectively	On census day 2001
2003	Rates of admission in Ireland for depression = 235.9 and 325.9 for men and women	2001 rates/100,000; 31% of total admissions = depression
2003	33% of admissions in Ireland = depressive disorders in 2002	2002 admission rate (all diagnoses) = 781.7
2003	59 children admitted in 2002 in Ireland	31% neurotic, 24% conduct disorder, 19% depressive
2004	Global Burden of Disease	Depression is fourth leading cause of disease burden, accounting for 4.4% of total DALYs in 2000; causes largest non-fatal burden (12% of all total years lived with disability worldwide)
2004	Lifetime prevalence of psychotic symptoms in BP = 40%	Grandiose delusions typify mania; doom/death in depression
2004	29% of admissions in Ireland for depression	12% were for mania
2005	30% of admissions in Ireland for depression	Admission rate for depression = 215.8/100,000 (mania = 89.7)
	4% of people have BP I or II disorder	Replication of NCS
2007	Depressive disorder accounted for 55%, anxiety disorders 30% and alcohol dependence for 15% of QALY loss on the population level	Finnish population study of those at least 30 years of age
2007	1-year prevalence for ICD-10 depression alone = 3.2% ¹²⁵⁸	Episodes of depression, 60 countries
2008	Childhood/adolescent BP onset twice as common in US as in Germany or Netherlands	This US study also found excess of childhood abuse and genetic/familial risk for affective disorders in the US patients (requires replicaton)
	24.1% of mood disorder cases used alcohol/drugs to relieve symptoms (BP = 41%)	US community study (N=43,093 aged 18 years or more)
		Excess comorbid anxiety and personality disorders associated with such self-medication
2009	The gap between men and women for MDD may be narrowing	WHO world study: this is related to changing female gender roles
2010	Median duration of BP I episodes = 13 weeks	219 subjects with this diagnosis
	BP I and II: depression and anxiety comorbid cross-sectionally and longitudinally; substance use disorders moderately associated with manic symptoms, and eating disorders with depressive mood	DSM-IV diagnoses; prospective latent analyses
	Major depression and GAD are 2 distinct conditions that frequently co-occur due to shared underlying trait	Australian study did not support artificial comorbidity produced by current diagnostic system (used NESARC data)

¹²⁵⁶ Disparate results in prevalence are at least partly explained by the absence of a clear cut-off point between normal low spirits and depressive disorder.

¹²⁵⁷ Reported lifetime prevalence of dysthymia varies from 1% to 12% with M:F ratios of 1.5-2.5.

¹²⁵⁸ Compare with angina (4.5%), arthritis (4.1%), asthma (3.3%), and diabetes (2%).(Moussavi ea, 2007)

BP, bipolar affective disorder. GH, general hospital. LP, lifetime prevalence. DALYs, disability adjusted life years. QALY, quality-adjusted life year. MDD, major depressive disorder. NESARC, National Epidemiologic Survey on Alcohol and Related Conditions. NCS, National Comorbidity Study in USA. WHO, World Health Organisation.
Irish rates are per 100,000 pop. 16 years and over.

Major depression is no longer considered to be rare in children and adolescents, although the prevalence increases with age: 0.3% in pre-schoolers, 1.8% in prepubertal children, 4.7-8.9% in adolescents¹²⁵⁹, 7% in general paediatric wards, 40% in paediatric neurology wards, and 27-59% in child psychiatry clinics. Comorbidity is extremely high in depressed children. Major depression may be more common in males before pubescence, a reverse in sex ratio occurring between the ages of 11-13 years. By 15 years it is twice as common in girls as in boys and this ratio persists thereafter.

The earlier that one develops major depression the more time one has to suffer from it and its effects.

Associations of earlier onset of depression (Zisook ea, 2007)

Never married
Poorer social/occupational function
Poorer quality of life/negative view of life
Increased psychiatric/medical comorbidity
More depressive episodes/suicide attempts
More severe symptoms and suicidal thinking in index episode

The average age of onset of BP disorder is about 22 years. There is no sound evidence to link it to a particular social class.

Admissions, Republic of Ireland (ROI)

Republic of Ireland

Broad category of 'depressive disorders'/100,000 population in 1987¹²⁶⁰ = 235; 21% of male and 41% of female admissions respectively

1992 admissions for depression = 23% in public psychiatric hospitals, 34% in private institutions, and 39% in general hospital units¹²⁶¹

All admissions with depression

1993	29% (33% of first admissions)
1994	27%
1995	28%
1996	26%
1999	30%
2004	29%

Anxiety is highly comorbid with depression in the community and mixtures of the two groups of symptoms are common in GP.¹²⁶² ICD-10 (but not DSM-IV) includes a subsyndromal category of 'mixed anxiety and depressive disorder' where the symptoms of both are mild, i.e. were the symptoms of anxiety and depression considered on their own they would not meet the threshold for either an anxiety or a depressive disorder. Drug abuse is more often associated with affective than with nonaffective psychosis in the US. Major affective disorder may carry a greater risk for tardive dyskinesia than does schizophrenia.(Prien and Gelenberg, 1989) This may relate to something inherent in the affective disorders or to intermittent treatment (as per 'drug holidays') or a relatively older age at onset of treatment. However, the association between tardive dyskinesia and affective disorder is inconsistent.(Chong & Sachdev, 2004) Various studies suggest an increased risk for tardive dyskinesia in schizophrenic patients with a family history of mood

¹²⁵⁹ Hazell (2007) gives a figure of 3-5% of adolescents.

¹²⁶⁰ Compared with 66 for mania and 165 for schizophrenia.

¹²⁶¹ Schizophrenia showed the opposite trend – 24%, 21%, and 14% respectively.

¹²⁶² In fact, such comorbidity 'is the rule (at some point) rather than the exception' (Deakin ea, 2001, p. 121) Analysis of a Swedish twin sample found that genetic factors for lifetime major depression and generalised anxiety disorder (GAD) were strongly correlated, more so in females.(Kendler ea, 2007)

disorders. Finally, tardive dyskinesia may worsen during depression and lessen during mania.(Chong & Sachdev, 2004)

Is depression becoming more common or are people less happy than heretofore? There have been reports of an increase in depression,(e.g. Compton ea, 2006) eating disorders, and alcoholism in the latter part of the twentieth century, a so-called 'age-period-cohort effect'. Various authors have commented on this finding and wondered if it can be explained by increased alcohol and substance use (not supported by Compton ea, 2006), programmes promoting increased awareness of mood disorders (McIntyre & Nathanson, 2010, p. 1), or a broadening of the concept of depression to include normal variations in mood and habits. Also, cross-sectional data do not translate well into longitudinal (read prospective) data because, e.g., of forgetting or ignoring of past episodes (perhaps undiagnosed) and selective mortality among those who experience severe depression.(Prince, 2008, p. 58) Evidence from the Stirling County Study are against any overall increase in depression during the 40 years since 1952.(Murphy ea, 2000) Even if there is a real increase in 'depression' it may not be explained by a genetical-biological model to the exclusion of socio-economic factors.(Andreasen, 2001, p. 239) Indeed, a Belgian study clearly shows that worsening socio-economic factors and depression are closely related.(Lorant ea, 2007)

Stigma

The RCPsych Defeat Depression Campaign 1992-1996 aimed to reduce stigma, assist GPs and other professionals in diagnosis and management, and to increase public awareness of the extent and treatability of depression. The mass media was employed and surveys of public attitudes¹²⁶³ were undertaken at various stages. People wanted counselling since this was viewed as being more effective than medication, the latter being viewed as addictive. The end point revealed some positive shift in attitude toward depression and medication.(Paykel ea, 1998)

Aetiology

'...the diagnosis of MDD [major depressive disorder] is only descriptive and likely consists of a number of syndromes with related symptoms'.(Lam & Mok, 2008, p. 11)

'These subsyndromal presentations of depression need to be distinguished from normal suffering....'(Ayuso-Mateos ea, 2010)

Depression superficially resembles such phenomena as tribal dominance and hibernation.

Freud postulated that depression ('melancholia') followed not an external loss, such as the demise of a loved one, but rather an internal loss, such as loss of a sense of personal identity or loss of belief in God. Advanced paternal age¹²⁶⁴ (Frans ea, 2008) and maternal age (Menezes ea, 2010) may be risk factors for bipolar affective disorder (BP) in the offspring, presumably by increasing the likelihood of genetic mutation. Early loss of a parent may increase the chances of later depression, but not all researchers have found a connection between early environment and adult affective disorder.(Rodgers, 1990) Indeed, early loss of parent has also been suggested as predisposing to anxiety disorder, bipolar disorder,(Mortensen ea, 2003) schizophrenia,(Agid ea, 1999) dissocial personality disorder, and substance abuse. It has also been suggested that it may lead to abnormal illness behaviour, the person learning to gain attention by complaints of ill health. Also loss of parents because of evacuation in wartime Britain does not seem to have led to an increase in affective illness in adulthood, whereas depression in adult life has been correlated with separation from parents because of marital discord and divorce¹²⁶⁵.(Tennant, 1988; Gilman ea, 2003)

¹²⁶³ Approximately 2000 representative people were used in each survey.

¹²⁶⁴ Advanced age of the father has been suggested as a risk factor for a number of complex neurodevelopmental disorders, e.g. schizophrenia, and autism spectrum.

¹²⁶⁵ Ted Dinan of Cork delivered a talk in Dublin (November 6, 2008) on certain biological aspects of depression (*Depression: Studies from Cradle to Grave*): Separation of rodent pups for 3 hours per day (kept in warm cages) for a period after birth led to raised corticosterone levels together with behavioural change and differences in colonic flora. Male pups were more susceptible to separation experiences than were their female counterparts. In a non-psychiatric population, desertion by or death of parents was found to be associated with raised cortisol level in adulthood. Increases in tumour necrosis factor-alpha (TNF α), a pro-inflammatory cytokine have been reported in maternally separated animals. ACTH shows a blunted response to CRH in major depressive disorder (MDD). Chronic elevation of CRP (**C-reactive protein**) is associated with raised mortality from cardiovascular disease. Baseline CRP is raised in melancholic depression and SSRIs tend to decrease CRP levels. Also elevated during depression are **IL6** and TNF α . Depressives have particular difficulty bringing cortisol levels down after such levels rise. Topical steroids blanch skin but such blanching is diminished in severe depression, suggesting reduced sensitivity of steroid receptors – this may explain why depressives rarely develop a Cushingoid appearance despite hypercortisolaemia. Depression occurring at any time increases the risk for heart disease to the same degree as do smoking 20 cigarettes/day (2-3 times the risk for myocardial infarction [MI]), diabetes, or lack of exercise. Toll-like receptors, originally found in *Drosophila*, recognise patterns (pathogen-associated patterns) and have various functions, e.g. activation of pro-inflammatory pathways and apoptosis. TLR4 recognises gram-negative bacteria. TLR4 is also raised in MI. Other toll-like receptors recognise viruses. Stimulation of toll-like receptors leads to a rise in FF- κ B leading in turn to cytokine release. TLR4 is

It has also been proposed that unsatisfactory care in childhood *after* loss of the parent is the crucial factor and that adequate substitute parenting may be protective. Young monkeys who are separated from their mothers vary in the intensity of their responses, e.g. those with more rejecting mothers are most disturbed by the loss. (Hinde & Spencer-Booth, 1970) Osler *et al.* (2005) in a Danish study spanning 1969-2002, failed to find any association between birth dimensions (birth weight and ponderal index – the latter was employed as a proxy measure of intrauterine growth and = birth weight in kilograms divided by [birth length in metres]³) and risk of receiving a discharge diagnosis of depression. However, Costello *et al.* (2007) did find an association between low birth weight and depression in adolescent girls but not boys. Also, Nomura *et al.* (2007) found that perinatal problems (low birth weight, preterm birth, small head circumference) in Baltimore babies increased the risk for later depression, suicidal ideation and high blood pressure.

Another pathway to adult depression in women who had inadequate parenting in childhood might be via premarital pregnancy, an unsupportive husband, and marital disharmony and lack of social support. The sociologist Brown's famous work related depression to being a young working class mother who has young children, a non-confiding relationship with her partner, and not even a part-time job. However, Romans *et al.* (1993) in their Otago study found that marriage and child care were not risk factors for non-psychotic psychiatric disorder in women. Bifulco *et al.* (1991), again in a study of working class mothers, found an association between sexual abuse prior to age 17 years and case depression. Such abuse was also associated with having been divorced or separated or never having married or cohabitated. Child physical abuse and neglect were related to later adult major depression, but child sexual abuse (CSA) was not so related in a study by Widom *et al.* (2007) CSA might be linked more securely to depression in adult women if abuse was severe, with penetration or attempted penetration, although its specificity for depression is doubtful. (Bulik *et al.*, 2001; Gershon *et al.*, 2008) Enns *et al.* (2006) found that CSA and multiple adversities (abuse, deficient parental bonding, parental psychopathology) were strongly associated with future suicidal behaviour. Garino *et al.* (2005) looked at 100 patients at an academic specialty centre for the treatment of bipolar disorder and found that severe childhood abuse occurred in about half of the sample and was associated with early age of illness onset; severe emotional abuse was associated with later drug misuse and recent rapid cycling; severe CSA was linked to lifetime suicide attempts; and multiple forms of abuse was associated with a graded increase in risk for attempted suicide and rapid cycling. Conus *et al.* (2010) found that reports of sexual and/or physical abuse were common among bipolar I patients with a first episode of psychotic mania.¹²⁶⁶ Marital disruption may lead to a first episode of depression in either sex. (Bruce & Kim, 1992) CSA may lead to longterm dysregulation of the hypothalamo-hypophyseal-adrenal axis. Mothers of twins, especially if one twin dies subsequently, may be more prone to depression than mothers of closely spaced singletons. (Thorpe *et al.*, 1991)

One study of women (Kendler *et al.*, 1993) found that the strongest predictors (in order of strength of prediction) of liability to suffer an episode of major depression were stressful life events, genetic factors, a personal history of major depression, and neuroticism. Kendler and co-workers (Fanous *et al.*, 2007) concluded that neuroticism may be a vulnerability factor (but not directly causative) for major depression in men, but that major depression may cause neuroticism.

Depression may be more likely if the personality is obsessional or cyclothmic although not all findings agree. Low self esteem may be more relevant in unipolar than in bipolar patients, (Pardoen *et al.*, 1993) although not all authors agree. (Hirschfeld *et al.*, 1986; Jones *et al.*, 2005) In a general population survey of women who had been depressed for at least 12 months, Brown *et al.* (1988) found that events with a promise of a better future often led to an alleviation of symptoms.

Seligman's¹²⁶⁷ learned helplessness model (Seligman & Maier, 1967) suggests the depressive has learned that nothing one does affects the turn of events and so become like the dog who cannot avoid electric

increased in colonic mucosa in animals deprived of their mothers for a time after birth. Early life stress programmes neuroimmune and neuroendocrine systems. Negative life events trigger events in those who experienced early-life trauma. MDD has a pro-inflammatory phenotype that increases the risk for cardiovascular disease.

There is evidence (Gimeno *et al.*, 2009) that baseline C-reactive protein and IL6 predict cognitive symptoms of depression at follow-up.

¹²⁶⁶ The reader must be wary of drawing conclusions from such correlations. The connection could be causal, spurious, secondary to symptomatic (of BP disorder, secondary alcohol use, etc) parents or offspring (or both), or no more common than in the general population. Future research should address these issues.

¹²⁶⁷ Martin E P Seligman (b. 1942, Albany, NY), Professor of Psychology in Philadelphia, known for 'learned helplessness' and 'positive psychology'.

shocks, just lying there and taking it¹²⁶⁸. Implants of 5-HT-containing pineal tissue and catecholamine-containing adrenal medullary tissue into the frontal cortex of rats may protect them against developing learned helplessness under stress. (Sagen ea, 1990) However, there is no evidence to allow us to deduce a cognition of learned helplessness in lower animals and electric shocks may be non-specific stressors. We cannot capture the human conceptualisation of events, i.e. the same event may evoke widely different emotions in humans because of the different meanings applied by individuals, so-called *attributional style*. Interestingly, Isaacowitz and Seligman (2001) found that pessimists and optimists among older people in the community were at increased risk for depression, the latter being at greater risk for depression whereas the former were more likely to have persistent depression; taking an objective view may be the most protective strategy.

A few cases seem to use 'depression' for manipulative reasons, to gain sympathy, test others, or gain help. A number of studies have linked relapse of depressive illness to life events. Classically, losses (exit events)¹²⁶⁹ precede depression, whereas threatening events precede anxiety. An excess of exit events during the course of a depressive episode may precipitate a suicidal or parasuicidal act. The only truly rigorous approach to examining the effects of life events on the risk for depression is to assess their frequency before the onset of a first episode of the disorder. This would require massive numbers of potential patients. In a study conducted by Dolan ea, (1985) antecedent life events were associated with first episodes of depression and with greater severity of illness, but life events did not distinguish endogenous (DSM's melancholia and ICD's depression with somatic symptoms) from neurotic (depressive neurosis in DSM-III-R, dysthymia in DSM-IV) cases, and there was no relationship between life events and DST status. However, urinary free cortisol levels were higher in those patients with life events. Also, the timing of episodes in relation to psychological stress was more apparent in non-endogenous than in endogenous depressions in a study conducted by Frank ea. (1994) Keller ea (2007) found that different adverse life events were associated with distinct patterns of depressive symptoms: death/romantic breakup with severe sadness, anhedonia, appetite loss, and (for romantic loss) guilt; chronic stress (and to some extent failure) with fatigue and hypersomnia; and, when no adverse event was reported, there were fatigue, appetite loss, and thoughts of self-harm. Kasen ea (2009) found that childhood adversity, earlier high levels of negative life events and marital stress and a more rapid increase in marital stress increased the odds of major depression in women at average age of 60 years. Ambelas (1987) reported that young first admission manics had had a significant excess of life events (less important for older first admission manics) and that later episodes were precipitated by life events of much lower stress value. Life events could lead to help-seeking behaviour rather to illness *per se*¹²⁷⁰. Anyway, they are not specific to affective disorders. Life events may only be significant as precipitants for the earliest episodes of bipolar disorder, the condition apparently becoming autonomous thereafter¹²⁷¹. (Not all researchers found that later episodes of bipolar disorder [BP] were non-reactive to stress. [Hammen & Gitlin, 1997] Also, the likelihood of PTSD is increased in bipolar spectrum disorder, the combination significantly worsening social functioning. [Neria ea, 2008] Not all studies found worsening of BP (perhaps due to a kindling effect) over time¹²⁷². [Baldessarini ea, 2003]) They might also be due to the earliest stages of illness rather than causing or precipitating it. (Pardo ea, 1996) Also, the effects of life events in increasing liability to mood disorder in children of bipolar disorder parents slowly diminish with the passage of time.¹²⁷³

¹²⁶⁸ Seligman continued his experiments on college students who were asked to solve insoluble puzzles.

¹²⁶⁹ Harris (2001) states that losses that involve humiliation or entrapment are especially potent in precipitating depression and anything that instils hope (fresh start) may promote remission. Certainly, being jilted by a romantic partner may lead to dysphoria whereas this may improve if the relationship resumes, a phenomenon not uncommonly seen among overdosing teenagers in emergency departments.

¹²⁷⁰ A similar argument has been made for the excess of depression in women, i.e. that they seek help more often than men do.

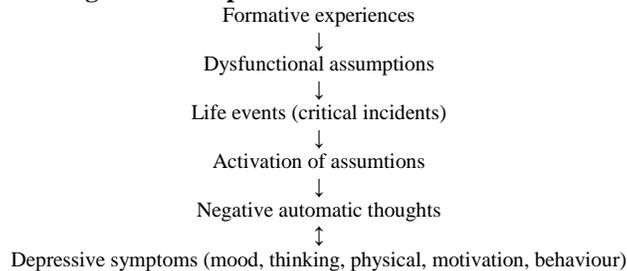
¹²⁷¹ Corbule (2007) reported similar findings for DSM-IV unipolar major depression (ACTUEL survey, N = 13, 377, 66.4% females), although the author admits that the retrospective nature of the study left it open to increased rating bias.

¹²⁷² Some experts do not accept that BP gets worse with time and suggest that the finding that it does get worse may be an example of *Slater's fallacy*: Writing in German in 1938, the British psychiatrist Eliot Slater (1904-1983) reanalysed Emil Kraepelin's data and realised that faster cycling patients (more episodes) were disproportionately represented when pooled samples were used. This problem is avoided when subjects are followed up individually or when groups matched for episode counts is used.

¹²⁷³ Decay of 25%/year. (Hillegers ea, 2004)

Beck's cognitive theory suggests that depression will happen because the person views the future, the world and themselves in a negative way.¹²⁷⁴

Cognitive therapy view of the genesis of depression



Le Masurier ea (2007) found that relatives of patients with major depression show subtle biases when processing emotional information, e.g. they recognised a fearful face faster than controls. Brotman ea (2008) found that bipolar and people at-risk for that disorder (all aged 4-18 years) had equal problems in identifying facial emotions, suggesting that deficits in labelling facial emotions might be a risk factor for bipolar disorder. Schenkel ea (2008), building on earlier work demonstrating theory of mind (ToM¹²⁷⁵) deficits in manic and euthymic bipolar (BP) disorder patients, found that paediatric BP patients also performed poorly in this regard. Moratti ea (2008) found that (female) major depressives demonstrated hypofunction of the right temporoparietal cortex relative to controls during emotional arousal induced by looking at pictures.

A battle has raged since the 1960s when Flor-Henry suggested that affective disorder be linked to the non-dominant hemisphere. His patients were awaiting temporal lobe surgery, were small in number, and were mainly bipolar. Goswami ea (2007) reported that euthymic BP patients had more (and non-age-related soft neurological signs (SNS) than normal controls (whose scores increased with age), but less than the numbers reported for schizophrenia.

One idea is that depression represents a sub-ictal or inter-ictal phenomenon with a focus in the tempero- limbic system. Rapid-cycling BP, which is strongly associated with female sex, might come into this sphere, the latter often responding to anticonvulsants (although this is less certain than was previously believed: Calabrese ea, 2005a) or, e.g. a combination of valproate and lithium. Bradyphrenia, or cognitive slowing, in Parkinson's disease, and psychomotor retardation in depression, may both be due to a common dysfunction of extrastriatal ascending dopaminergic systems. In fact, there is some evidence for increased postsynaptic DA responsivity in BP disorder.(Anand ea, 2000)

An imbalance between rewarding sensations (subserved by noradrenaline) and punishment-like responses (5-HT) in the brainstem-diencephalon might lead to depression. A more modern concept is that there may be a hypoactive reward system subserved by DA in major depression¹²⁷⁶ but an increased response to oral dextroamphetamine.(Tremblay ea, 2002; Tremblay ea, 2005)

Direct evidence for catecholaminergic dysfunction as a trait in major depressive disorder (MDD) comes from a study (Hasler ea, 2008) where unmedicated MDD subjects (n = 15) in full remission and healthy controls (n = 13) were given alpha-methylparatyrosine to induce catecholamine depletion. Depressive and anhedonic symptoms were greater in the patient group. Elevated activity in limbic-cortical-striatal-pallidal-thalamic circuitry on PET were related to the induced symptoms.

¹²⁷⁴ *Criticism of Beck*: It is a controversial point as to whether low self-esteem/negative self-schema comes before or after the experience of depression.(Evans ea, 2005; Ball ea, 2008) Farmer ea (2001) applied the *Dysfunctional Attitude Scale* to depressed subjects before and following recovery and concluded that dysfunctional attitudes were more to do with being depressed than to a familial vulnerability to depression. Harmer ea (2009) found that negative affective bias was relieved by a single dose of reboxetine despite no relief of subjective depression; no such effect was found with placebo. Brain activation (fMRI) in depressed subjects who are expecting events of uncertain emotional valence has been shown to be the same as when expecting negative (but not positive) events.(Herwig ea, 2010) This, of course, does not distinguish between state and trait.

¹²⁷⁵ This refers to an ability to infer what another person is thinking and feeling.

¹²⁷⁶ Dopamine (DA) levels in brain are increased in a number of circumstances, e.g. sexual arousal, ethanol, heroin, and cocaine.

5-HT content in the brain is normally lower in men and older age than in women and youth. It is also dependent on diet (cholesterol, fatty acids, and tryptophan) and alcohol, the latter reducing 5-HT transporter function in the prefrontal cortex. (Malone, 1999) Reduced levels of the 5-HT transporter relative to controls have been reported in depression (including bipolar depression: Oquendo ea, 2007a), in euthymic bipolar I but not euthymic bipolar II patients (Chou ea, 2010), and in suicides. (Owens & Nemeroff, 1998)

Insulin resistance is a determinant of free fatty acids in blood, which in turn are important in tryptophan metabolism and brain 5-HT concentrations. According to Lawlor ea, (2003) people with insulin resistance may therefore have increased 5-HT concentrations and be less prone to depression. However, Timonen ea (2005) found that people with increased insulin resistance seen prior to a diagnosis of diabetes mellitus had greater severity of depression. Andersohn ea (2009) looked at patients receiving at least one new prescription for an antidepressant and found that longterm TCAs and SSRIs in at least modest doses were associated with an increased risk of diabetes; weight gain was not systematically recorded and if drugs were primarily prescribed for atypical depression the results may overestimate the link; and control subjects were matched to case subjects on age, sex and year of cohort entry rather than consisting of equally depressed patient not receiving at least one new prescription for an antidepressant in equivalent dosage for the same duration (assuming everyone takes the drug as prescribed). A prospective Australian study of people aged at least 65 years (Atlantis ea, 2009) found that depressive symptoms more than doubled the risk of developing diabetes regardless of antidepressants.

Schildkraut, in 1965, was the first to suggest the monoamine hypothesis of affective disorders. Parachlorophenylalanine, which selectively depletes 5-HT, was reported to reverse the antidepressant effects of both TCAs and MAOIs, an effect not found with the catecholamine-depleting agent α -methyl-paratyrosine. These findings were interpreted as favouring a serotonin deficiency basis for depression over a catecholamine depletion hypothesis. However, more recent work suggests that depletion of 5-HT or noradrenaline, whilst not causing depressive symptoms in normal people, increases vulnerability to relapse in people treated with either 5-HT- or noradrenaline-selective reuptake inhibitors respectively. (Delgado ea, 1999; Berman ea, 2002) Parsey ea (2006) found low serotonin transporter binding potential in the amygdala and midbrain of subjects during a major depressive episode compared to healthy controls. There is some evidence linking the genotype of the serotonin transporter gene-linked promoter region to onset of major depression following multiple adverse events. (Wilhelm ea, 2006) Ohara ea (1999) reported a common polymorphism of the variable-number tandem repeat within the serotonin transporter gene associated with major depression and anxiety disorders, particularly generalised anxiety disorder. Platelet imipramine binding (may serve as a measure of presynaptic 5-HT functioning) sites were reported as significantly reduced in depression and this seemed to be independent of treatment with drugs. Plasma NA levels were reported as increased in major depressive disorder, the levels falling if electroconvulsive therapy (ECT) were administered. Of course, this finding may have been due to increased sympathetic tone in depressed patients. When noradrenergic (NA) neurones are destroyed in experimental models drugs affecting the 5-HT system do not have their usual effects, and *vice versa*. This suggests that aetiology may be more complex than single monoamine paradigms might suggest. (Willner & Mitchell, 2002)

One theory of the mechanism of action of antidepressant drugs is that in depression receptors are supersensitive (upregulated). Treatment increases the amount of neurotransmitter acutely but the effect of this over time is to desensitise (downregulate) receptors. Downregulation correlates with clinical effect. There are a number of lines of evidence suggesting widespread GABAergic abnormalities in mood disorders. The most impressive are those that demonstrate reduced concentrations of GABA in plasma, CSF, and cerebral cortex in depressed patients.¹²⁷⁷ MRS suggests abnormal reductions in GABA and glutamate/glutamine¹²⁷⁸ in prefrontal regions in major depression, probably related to reduced glial cell density in these areas. (Hasler ea, 2007) Leonard (2003, p. 36) expressed surprise at the finding of reduced concentration of GABA in depression because of the lack of evidence for cortical excitability in that disorder and suggests that it might reflect decreased availability of glutamate, the excitatory precursor of GABA. A combined fMRI/MRS study (Walter ea, 2009) suggests that aberrant activation patterns of the pregenual anterior cingulate cortex in depression with anhedonia is related to defective glutamatergic

¹²⁷⁷ For a review see Sanacora (2002)

¹²⁷⁸ Ionotropic glutamate receptor genes GRIA3 and GRIK2 may be linked to suicidal ideation arising during citalopram treatment of major depression. (Laje ea, 2007)

metabolism. Cortical inhibitory deficits may play a role in the pathophysiology of major depressive disorder (MDD) according to Levinson *et al.* (2010): they suggest that GABA-B neurophysiological deficits are closely associated with MDD and that greater disorder severity is selectively associated with GABA-A receptor-mediated inhibitory deficits.

Pleasure is associated with DA release in the brain reward system¹²⁷⁹. Bupropion¹²⁸⁰, amineptine,¹²⁸¹ and nomifensine¹²⁸² are the main dopaminergic antidepressants. Pramipexole (Mirapexin), used for Parkinson's disease, is a D2/3 agonist with preferential D3 binding affinity. Whiskey and Taylor (2004) reviewed the literature on the use of pramipexole in depression (unipolar and bipolar) and concluded that whilst the data appear promising further research is required.

Meyer *et al.* (2006), using PET, found increased MAO-A levels in many brain areas in unmedicated depressives. Also, PET has demonstrated elevated MAO-A binding in major depressive disorder following SSRI treatment. (Meyer *et al.*, 2009)

Hypothalamic-pituitary-adrenal (HPA) axis overdrive might lead to central monoaminergic changes in susceptible people under chronic stress, the high levels of glucocorticoid receptors on such central neurones perhaps mediating the alterations.¹²⁸³ Perhaps old-age depression with cognitive impairment might be due to cortisol-induced neuronal damage, although this is still controversial. (Ebmeier & Kronhaus, 2002) Reduced levels of dehydroepiandrosterone (DHEA)¹²⁸⁴ may contribute brain damage due to cortisol (DHEA may be useful in non-major depressed HIV/AIDS cases: Rabkin *et al.*, 2006). It has also been suggested that change in peptides¹²⁸⁵ (that are involved in stress adaptation) in brain areas linked to emotional responses like the amygdala may precipitate depressive illness. It has been asserted that the reason for developing psychotic features in the context of a depressive episode may be enhancement of dopaminergic activity by glucocorticoids. Circulating corticosterone levels modulates the density of 5-HT1A receptors in animals. An excess of cortisol secretion might attenuate limbic 5-HT1A receptor function, predisposing to depression¹²⁸⁶. Also, animal studies suggest that corticosteroid administration causes hippocampal cell loss¹²⁸⁷. Sheline *et al.* (2003) found that hippocampal volume decreased as the number of days of untreated depression increased. However, Lloyd *et al.* (2004) found that smaller hippocampi were associated with late-onset depression only and not with lifetime duration of depression. The authors admit that the latter is difficult to measure accurately and all the patients were on medication. Kronmüller *et al.* (2008) found that smaller hippocampi were associated with relapse of major depression and Chen *et al.* (2010) found that girls at high familial risk of developing depression had small hippocampi compared to those at low risk, i.e. that reduced hippocampal volume precedes depression. Hippocampal volume in depressed patients has increased following ECT. (Nordanskog *et al.*, 2010) Cervilla *et al.* (2004) found an association between incident depressive symptoms and baseline smoker status, low serum cholesterol levels, poorer cognitive function (esp. executive function), female gender and increasing age, but not with ECG evidence of ischaemia or arrhythmia, various blood pressure measurements and body mass index. However, despite sustained hypercholesterolaemia¹²⁸⁸, depression does not lead to Cushing's syndrome. Also, HPA axis dysfunction may be a manifestation of acute but not chronic depression. (Watson *et al.*, 2002) Such dysfunction may also play a part in treatment resistance in depression. (Jurueña *et al.*, 2009) It has been suggested that antidepressants and the mood stabilising drugs up-regulate glucocorticoid receptors, so

¹²⁷⁹ See Dunlop and Nemeroff (2007) for review of review of reduced dopaminergic neurotransmission in major depression.

¹²⁸⁰ Used for smoking cessation.

¹²⁸¹ Has a propensity for addiction.

¹²⁸² Carries risk of acute haemolytic anaemia and intravascular haemolysis.

¹²⁸³ Summers *et al.* (2006) found cognitive deficits to be more severe and pervasive in bipolar II than in bipolar I patients, which the authors believe suggests that recurrent depression is more cognitively damaging than are manic attacks.

¹²⁸⁴ A natural cortisol antagonist.

¹²⁸⁵ E.g. corticotrophin releasing factor (CRF).

¹²⁸⁶ Various changes may explain delayed onset of antidepressant action: time required to desensitise presynaptic 5-HT1A autoreceptors and down-regulate postsynaptic alpha-adrenergic and 5HT2 receptors.

¹²⁸⁷ The frontal lobes contain mainly glucocorticoid receptors whilst the hippocampus contains both mineralocorticoid and glucocorticoid receptors – these regions may have some inhibitory action on HPA activity; mineralocorticoid receptors bind corticosteroids with a higher affinity than do glucocorticoid receptors. (Lupien, 2002)

¹²⁸⁸ The literature is inconsistent, e.g. Fiedoronicz *et al.* (2010) conducted a follow-up (median 20 years, max 25 years) of patients who had a fasting total cholesterol evaluation at intake: low cholesterol among bipolar patients (N = 65) predicted a higher proportion of follow-up weeks with manic but not depressive symptoms and cholesterol did not predict depressive symptom burden among unipolar depressives (N = 66).

restoring normal glucocorticoid function in mood disorders.¹²⁸⁹ Also, there is evidence that antidepressants induce neurogenesis,(Santarelli ea, 2003) although this may be a chronic rather than acute effect.(Malberg ea, 2000) According to Duman,(2004) antidepressants cause increased coupling of Gs protein to adenylyl cyclase, increased levels of cAMP-dependent protein kinase, and decreased levels of CREB; the time course of increased cAMP-CREB signalling depends on chronic treatment¹²⁹⁰; activation of CREB increases target gene expression (e.g. BDNF¹²⁹¹) that exert trophic actions on target neurones with increased cell survival and function. In contrast, stress causes a dramatic downregulation of BDNF¹²⁹² in the hippocampus.

Cotter and Pariante (2002) suggest that the pathological changes reported in schizophrenia, bipolar disorder and major depressive disorder¹²⁹³ differ only quantitatively rather than qualitatively¹²⁹⁴. They suggest that the common cause may be (stress-related) glucocorticoid-induced damage. However, DST non-suppression rates in schizophrenia¹²⁹⁵, whilst unsurprisingly higher than in the healthy population, are 'much lower than that described in depression'. They point out that the reduction in hippocampal volume reduction seen in cases of Cushing's disease is reversible after normalisation of cortisol levels and express the hope that neuroprotective therapies may be developed for the psychiatric disorders under consideration.

Whilst autoimmune thyroiditis occurs in about 15% of depression it may occur in up to 50% of cases of rapid cycling bipolars. Absence of the normal TSH surge during the night have been reported in depression; sleep deprivation restores this surge and raises levels of T₃ and T₄.(Arce ea, 2003, p. 228) Transthyretin, a protein made in the choroid plexus, is more important for T₄ than for T₃ transport across the blood-brain barrier. CSF transthyretin levels may be reduced in depression, a situation that has led to the theory of depression as a state of 'brain hypothyroidism' in the presence of normal peripheral thyroid hormone concentrations.(Hatterer ea, 1993) However, major depression may be almost as common in hyperthyroidism (31%) as in hypothyroidism (40%) (Rouchell ea, 1996) and general population studies of hypothyroidism did not find an excess of depression.(Engum ea, 2002)

Brain-derived neurotrophic factor (BDNF) is important in maintaining neuronal viability, including hippocampal plasticity. BDNF binds to the tyrosine kinase receptor TrkB. Under stress, BDNF is repressed. This could conceivably lead to atrophy and perhaps to apoptosis in hippocampal neurones. Depression might be the result. Carriers of the Met-BDNF allele may be at particular risk to develop small hippocampi and depression.(Frodl ea, 2007) Childhood adversity of various types have an impact on depressive symptoms in adulthood. Also, child sexual abuse may be associated with a stronger likelihood of depressive symptoms in adults who carry the Met-BDNF allele (v. the Val/Val allele) or in S (v. the LL group) carriers of the 5-HTTLPR polymorphism (5-HTT gene).(Aguilera ea, 2009)

The three neurokinins (tachykinins) are substance P (11 amino acids)¹²⁹⁶, neurokinin A (NK-A, 10 amino acids), and neurokinin B (NK-B, 10 amino acids). Since antagonists of substance P did little for pain but had an inconsistent beneficial effect on depressed mood, and since substance P is present in brain areas such as the amygdala that may be important for the emotions¹²⁹⁷, it has been suggested, but not yet proven,

¹²⁸⁹ Suicidal events among treatment-resistant adolescent depressives were associated with FKBP5 polymorphisms (rs1360780TT and rs3800373GG) in a relatively small study (Brent ea, 2010) without a placebo condition. FKBP5 codes for a protein causing glucocorticoid receptor subsensitivity.

¹²⁹⁰ Consistent with the delayed onset of an antidepressant response, although such delay may be much shorter than is generally believed.(Tylee & Walters, 2007)

¹²⁹¹ The so-called *network model* suggests that depression is due to interneuronal communication difficulties and that antidepressant drugs improve such communication. In animals antidepressant drugs increase neuronal turnover and sprouting of synapses. ECT and antidepressant drugs increase BDNF levels (via CREB activation) which stimulates local sprouting of axons. Umene-Nakano ea (2009) found relatively low serum BDNF levels in depressives with or without alcohol dependence. Downregulation of BDNF expression in suicidal subjects may be an epigenetic phenomenon as a result of gene-specific increase in DNA methylation.(Keller ea, 2010)

¹²⁹² Delta-opioid receptor agonists resemble antidepressants in rodents. They increase brain BDNF levels. Sustained sadness decreases capacity for cortical mu-opioid receptor binding. Early reports suggested that opiates might relieve depression (Weber & Emrich, 1988), but hard evidence is lacking. Also, there is some evidence that variation in the mu-opioid receptor gene may influence rates of response to antidepressant drugs (Garriock ea, 2010), although this effect could be either via a placebo or pharmacological action.

¹²⁹³ E.g. enlarged ventricles and smaller hippocampi and frontal brain volumes, as well as reduced dendritic spine density, smaller neurones, a reduction in synaptic proteins, and a deficit in glia.

¹²⁹⁴ Except that the amygdala may be specifically enlarged in bipolar disorder, which might be due to drug treatment.

¹²⁹⁵ Mean of 20% from different studies.

¹²⁹⁶ P standing for powder, the original form in which it was isolated.

¹²⁹⁷ Substance P is elevated in CSF in depression and in PTSD.(Geraciotti ea, 2006)

that blocking neurokinin receptors may improve mood. Ernst et al (2009) found a reduction of tropomyosin-related kinase B (TrkB.T1)¹²⁹⁸ expression in the frontal cortex of a subpopulation of suicide completers that was associated with the methylation state of the promoter region.

Depression as an inflammatory disorder- speculative theory (Leonard, 2007)

In depression:

- Neuronal repair is slowed
- Hippocampal atrophy
- Glia and neurones in prefrontal cortex adversely affected
- Glucocorticoid-mediated cell loss probably involved
- Rise in pro-inflammatory cytokines (PICs) may play a role
- Interferon-alpha, a PIC, may cause depression
- Anterior cingulate is rich in 5-HT transporters (and other neurotransmitters)
- BCL-2 (anti-apoptotic protein) and BDNF genes are important in neuronal plasticity and survival
- BDNF is reduced in depression
- Physical exercise improves depression (not necessarily true: Walker et al, 2010) and promotes rat hippocampal neurogenesis
- Stress reduces hippocampal cell proliferation
- IL-1, IL-6 (potent HPA axis activator), and TNF-alpha are increased in depression/chronic stress and induce depression in rats (less so if on chronic antidepressant treatment)
- Reduction of high cortisol feedback on brain with metyrapone decreases depression
- Chronic antidepressant treatment switches on neurogenesis/repair genes with some benefit
- PGE2 (via COX2 activity) is increased in depression (reduced by antidepressant drugs) – COX2 inhibitors being tested in depression models
- Antidepressants decrease indoleamine dioxygenase (IDO) which converts tryptophan to kynurenine
- The hallucinatory agent and glycine B antagonist ketamine relieves depression for 2 weeks after one dose but safer drugs are needed
- Lithium inhibits brain glycogen synthase kinase-3 (GSK-3)¹²⁹⁹ leading to diminished apoptosis and improved brain repair

Theory: In depression, is tryptophan changed to kynurenine instead of tryptophan in presence of PICs, the latter induced by psychological and physical stress, leading to neurodegeneration/depression? Thus:

- (a) ↑ kynurenine in depression → quinolinic acid (neurotoxic) in microglia → astrocyte and then neurone death
- (b) Kynurenine → kynurenate (neuroprotective) is ↓ in depression

There is a suggestion that deficiency of orexins/hypocretins might have a role in causing depression. (Taheri & Hafizi, 2002)

Could infection in utero cause later adult depression? Looking at patients with 'major affective disorder', Machón et al (1997) of Helsinki found an increased likelihood of exposure to an epidemic of influenza (A2/Singapore virus) during the second trimester compared to controls.

Cotter et al (2001) found a reduction in reduced neuronal size and glial cell density in the anterior cingulate cortex of major depressives at postmortem. Relatively small cingulate volumes in children and adolescents with bipolar disorder have been reported, (Kaur et al, 2005) suggesting that such may be the case from early in the illness course.

Geomagnetic storms have been suggested as a cause of depression in susceptible individuals. They might desynchronise pineal circadian rhythms or they might disrupt pineal melatonin synthesis¹³⁰⁰ via actions on serotonergic or adrenergic systems. Such storms could, according to the theory, act on cell membrane permeability, cause increased calcium channel activity, or the retinal rods could act as magnetoreceptors. The circadian timing system may have a role in depression. Light acts on the suprachiasmatic nucleus (SCN) via illuminance-measuring photoreceptors in retinal ganglion cells. The SCN affects the pineal gland via the paraventricular nucleus¹³⁰¹ and this then drives nocturnal melatonin synthesis, the latter being

¹²⁹⁸ Normally, TrkB.T1 is the only TrkB isoform expressed in astrocytes. BDNF-TrkB signalling may be linked to depression and suicide. The TrkB.T1 variant mediated BDNF-induced calcium signalling through astrocyte networks. TrkB.T1 is upregulated by antidepressants.

¹²⁹⁹ GSK3β may have a role in determining regional gray matter volume in the temporal lobe in major depression. (Inkster et al, 2009)

¹³⁰⁰ Melatonin shows significant night-time secretion. Melatonin secretion is fairly constant within individuals but varies widely between individuals.

¹³⁰¹ The paraventricular nucleus neuroendocrine cells have regulatory effects on pituitary hormones; there are also projections from this nucleus to the autonomic nervous system. (Buijs et al, 2003)

suppressed by light. The SCN affects preoptic area, raphe nuclei, and dorsolateral and posterior hypothalamus (all involved in regulating sleep) as well as peripheral 'clocks' in various tissues. Lam ea (2001) suggests that circadian abnormalities lead to sleep disorders (e.g. phase shifts), serotonin abnormalities lead to disorders such as OCD, but combined circadian-5-HT (hypofunction) abnormalities lead to major depression (MDD) or seasonal affective disorder. Turnover of central 5-HT is normally much greater in summer than in winter, as is placebo response in depression. Light therapy added to an SSRI may speed up response in non-seasonal MDD. Also, light therapy may be useful in the treatment of depression lasting more than two years. (Wirz-Justice, 2005) Contraindications to light therapy are relative (retinal photosensitising drugs such as lithium, thioridazine and melatonin; disease of retina; macular degeneration).

Mutation in the mouse 'CLOCK' gene, a core circadian clock gene, is thought to induce mania-like behaviour. (Roybal ea, 2007) However, a study from Japan (Kishi ea, 2009) failed to find any association between the 6 tagging SNPs in CLOCK and bipolar disorder, major depressive disorder, or schizophrenia, although the authors wondered if a study using bigger numbers of patients might produce different results. The RAR-related orphan receptor beta (RORB) is altered in mice lacking the clock gene D-box binding protein (DBP). This has been suggested as a stress-reactive genetic animal model of bipolar disorder (BP). In a study of a paediatric cohort, McGrath ea (2009) found a positive association between 4 intronic RORB SNPs and the paediatric BP phenotype. These findings should be subjected to further research.

Pharmacological, pathological, pathochemical, and related genetic findings in depression (in roughly chronological order)

Reduced prolactin (P) response to fenfluramine (F) in endogenous depression; basal P levels reduced in bipolar (BP) v unipolar (UP) depression, and delusional v non-delusional depression, although there were no differences in P responses to F between these subgroups; basal cortisol (C) levels and C response to F did not distinguish between subtypes
No increase in cerebral glucose metabolism in drug-free, untreated major depressives (normal response is increased metabolism)

Higher lethality suicide attempts associated with lower P response to F

Major depressives (MD) had blunted P response to clomipramine

Tryptophan-deficient amino acid mixture (TDAAM) lowered mood only if there was a family history of major affective disorder

TDAAM evoked depression in women with past recurrent MD but currently in remission and drug free

TDAAM in remitted SAD during summer increases chances of return of depression

Euthymic, drug-free people with a history of MD become depressed if given α -methyl-paratyrosine (catecholamine depletion via tyrosine hydroxylase inhibition)

Since both TDAAM and α -methyl-paratyrosine reverse light therapy effects in SAD both 5-HT and catecholamines may be involved

Lithium may protect against TDAAM-induced mood changes or suicidality in BP disorder

Whole-blood tryptophan was lower in prepubertal child psychiatry in-patients with recent AS

Tryptophan hydroxylase U allele associated with attempted suicide in MD

Dieting reduces plasma tryptophan in females independent of mood status; unlike women with a history of depression, dieting

increased prolactin response to tryptophan in women without a history of depression

5-HT_{2A} receptor binding greater in prefrontal cortex (PFC) of suicides – this author agrees with the original researchers that this was due to overrepresentation of violent suicides; teenage suicides had increased levels of 5-HT_{2A} receptor, protein, and mRNA expression in PFC and hippocampus (suggesting emotional, stress, and cognitive elements)

Diffusely decreased 5-HTT (serotonin transporter sites) binding in prefrontal cortex (PFC) of major depressives and localised reduction in ventral PFC of suicides (PET study later showed reduced PFC glucose uptake in high-lethality attempted suicides with MD: Oquendo ea, 2003)

Impaired sensitivity of postsynaptic 5-HT_{1D} receptors that mediate growth hormone release demonstrated in melancholic depression

High plasma β -endorphin levels may be associated with more severe anxiety, phobia and obsessions and compulsions in the depressed

Life events might activate noradrenergic projections from brain stem to hypothalamus, secretion of CRF/ACTH/corticosteroids, and the action of latter at type II corticosteroid receptors in the brain, leading to depression

A blunted TSH response to TRH has been described in depression but is not specific to it

G proteins in mononuclear cells reduced in terms of function and quantity of G_s and G_i in proportion to depth of depression;

normalised with ECT and before mood lifted, predicting good response

Untreated patients with atypical winter depression had decreased G_s and G_i in mononuclear cells, normalising during summer or with light treatment

Increased CRF (CRH)-containing cells and CRH mRNA in paraventricular nucleus of hypothalamus in suicide victims

Increased intracellular calcium in platelets and lymphocytes in both phases of BP but not in UP, euthymic patients or controls

Increased Rap 1 (a protein kinase A substrate) in platelets of untreated euthymic BP, depressed BP, and manic patients, possibly reflecting a problem in cAMP phosphorylation system

Higher than expected prevalence of anti-thyroid antibodies in BP not due to lithium (but latter can exacerbate the process)

Reductions in components of the phosphoinositide signal transduction system in brains of suicides

Prolactin response to citalopram blunted similarly in both acutely ill and recovered major depressives (in favour of impaired 5-HT neurotransmission being a trait)

In MD, the cortisol response to citalopram blunted in ill patients but not in recovered subjects (may represent resolution of hypothalamic-pituitary-adrenal [HPA] axis dysfunction)

Acute tryptophan depletion impairs speed of information processing in first-degree relatives of bipolars and in controls; speed of information processing on a planning task impaired in relatives only; those with BP type I relatives had impaired planning and memory, independent of acute tryptophan depletion. 5-HT appeared to be involved in information processing, verbal and visual memory and learning processes.

Hippocampal sections looking at GAD (glutamic acid decarboxylase, involved in GABA synthesis): density of GAD65 and GAD67 mRNA-positive neurones reduced by 45% and 43% respectively in BP (only 14% and 4% respectively in schizophrenia); GAD65 mRNA-positive neurones in BP significantly diminished in sectors CA2/3 and dentate gyrus; GAD67 mRNA-positive neurones decreased significantly in CA4 in BP (but not in schizophrenia); authors suggest they have found a region-specific deficit in both these isoforms in BP. (Hekers et al., 2002)

Brain weight in suicides not significantly different from the general population.

Immunohistochemistry found increased cell adhesion molecule expression in grey matter of dorsolateral PFC (DLPFC) in postmortem tissue from elderly patient who had been diagnosed MD (suggestive of inflammation and consistent with ischaemia).

Neuroticism did not predict amount of mood change following acute tryptophan depletion in healthy volunteers (but it did moderate performance on a verbal fluency test).

Tryptophan hydroxylase A779 allele more common among deliberate self-harm subjects v controls.

No loss of 5-HT neurones and no neuritic pathology in dorsal raphe nuclei in older depressives, with or without comorbid Alzheimer's disease.

PET: medication-free MD had significantly decreased regional normalised trapping constant (K^*) of α - ^{11}C MTTrp, a proxy for 5-HT synthesis in cingulate cortex; difference in the cingulate cortex was statistically stronger in females; differences between MD and controls in normalised K^* values are mainly in anterior cingulate cortex.

Protein kinase C activity reduced in PFC and hippocampus of teenage suicides.

PET: tryptophan depletion induced transient return of depressive symptoms in remitted MD but not in controls; tryptophan depletion associated with increased regional use of glucose in orbitofrontal cortex, medial thalamus, ant and post cingulate cortices, and ventral striatum in remitted MD but not in controls; therefore, authors suggest that there is an underlying disease-specific 5-HT-related trait dysfunction in MD.

Beta-arrestin-1 levels reduced in white blood cells in depressives and elevated in rat brain by antidepressants.

Haplotype linkage of tryptophan hydroxylase 2 (TPH2 – encodes the rate-limiting enzyme for brain 5-HT synthesis) to suicide attempt and MD and to CSF 5-HIAA provides preliminary evidence of a functional locus potentially within a haplotype block at least 45 kb in size.

Presence of lifetime history of depression in Alzheimer's disease corresponds to increased Alzheimer-related neuropathological changes in the hippocampus – more pronounced if depression occurs early during the disease process.

Haplotype linkage analysis of TPH2 in UP and BP North Sweden isolates provides evidence of protective association in both disorders.

2-dimensional electrophoresis of DLPFC in scz, BP, and mentally normal controls to look for abnormal proteins: scz and BP had differences from controls; mass spectrometry identified 15 scz-associated and 51 BP-associated proteins; most affected were synaptic proteins in scz and metabolic and mitochondrial proteins in BP; majority of abnormally expressed synaptic-associated proteins in BP were isoforms of the septin family; findings are evidence for synaptic pathology in scz and metabolic dysfunction in BP.

Recovered male depressives have normal 5-HTT availability in brain areas considered important in pathophysiology of depression, e.g. anterior cingulate cortex.

MD, SERT-ss genotype and suicide contribute to an enlarged thalamus; the SERT-ss genotype and MD enlarge the pulvinar and limbic nuclei respectively; antidepressant treatments shrink the thalamus.

Link between childhood-onset depression and NTRK3 gene (neurotrophic tyrosine kinase receptor-3 on 15q).

In East Baltimore study 1 or 2 short alleles of serotonin transporter gene carried highest risk of first episode of MD but episodes tended to be relatively short.

Declarative memory impairment in young women at increased risk for depression may be partly related to increased cortisol secretion but no significant effect of 5-HTT allelic status on either memory or waking cortisol secretion was found.

Increased cortisol awakening response among those with current MD and those with remitted MD may indicate biological vulnerability to depression.

Effect of 5-HTTLPR (5-HTT promoter length polymorphism) on antidepressant response is SSRI specific, concentrated in males, and influenced by the single-nucleotide polymorphism rs2020933.

In adolescents at high risk for depression there were higher levels of cortisol in those with the short (s) allele of 5-HTT promoter (5-HTTLPR): s/s > s/l > l/l; subsequent depressive episode was increased in subjects with s allele and higher cortisol, and independently by depressive symptoms at entry, in both sexes.

Using small number of BP and MD cases and muscarinic selective radioligands differences were found between the two disorders.

During a cognitive test battery, near-infrared spectroscopy in BP suggested a discrepancy in PFC function between verbal versus non-verbal processing, indicating possible task-specific abnormalities in haemodynamic control of PFC.

Controlled post-mortem study found a decrease in pyramidal neuronal size in DLPFC in late-life depressives.

Postmortem study of anterior cingulate brain sections (BP, MD, schizophrenia, and controls) determined oxidative stress by analysing 4-hydroxynonenal (4-HNE), a major product of lipid metabolism; 4-HNE levels raised by 59%, 47% and not at all in BP, schizophrenia, and MD respectively; oxidative damage may contribute to BP and schizophrenia

Bulgarian study suggests that rs1800883, an SNP in HTRSA gene (variant of 5-HT5A gene) might confer susceptibility to BP

Postmortem study of habenular complex found significant volume reductions in depressives compared to normals and schizophrenia patients; for the right side, only the depressives had reduced neuronal cell number and cell area

Link between and NTRK2 gene¹³⁰² (neurotrophic tyrosine kinase receptor-2) and suicide attempts in major depression.

Impairment of mitochondrial complex I activity may be associated with increased PFC protein oxidation and nitration in BP.

In a study of polymorphisms in genes regulating the CRF (CRH)-releasing factor system, a SNP within the CRHBP locus is associated with response to citalopram and the T allele of this SNP is associated with poor response to this antidepressant in African Americans and Hispanics.

Significant reduction in neuronal density found in lateral septal nucleus in BP.

Notes: Fenfluramine, an amphetamine, is a serotonin agonist. Clomipramine inhibits serotonin reuptake. Whilst depression may be associated with a blunted P response to 5-HT, weight loss increases P response to 5-HT, and both these can cancel each other out, a point to be remembered when investigating the depressed patient who has lost weight! There have been reports of increased G protein measures in mononuclear cells in mania and in postmortem cerebral cortex in BP.

The 5-HTT binding potential varies with the seasons.(Praschak-Rieder ea, 2008)

The 5-HTTLPR gene variant of the serotonin transporter gene (SERT or 5-HTT) is comprised of a short (SERT-s) and a long (SERT-l) allele.

(DL) PFC, (dorsolateral) prefrontal cortex.

The EEG in depression shows reduced delta sleep and reduced REM latency, but increased REM density. Reduced slow wave sleep correlated strongly with recurrent affective disorder and may be a trait marker, whereas REM dysregulation is most marked during a depressed phase, especially early on in the episode.(Kupfer ea, 1991)

With regard to evoked potentials, psychotic BP patients have been noted to differ in the asymmetry of the M20 (this 20 msec latency somatosensory evoked field component is generated in the postcentral gyrus) from BP patients without psychosis.(Reite ea, 1999) Another study found that relatives of BP patients have reduced P300 amplitude and prolonged P300 latency.(Pierson ea, 2000) Results from a Maudsley bipolar twin and family study (Hall ea, 2009) suggest that auditory P300 amplitude and latency components (but not mismatch negativity) are valid endophenotypes for psychotic BP. Another study (Patterson ea, 2009)¹³⁰³ suggests that the P85 may be an endophenotypes for BP I disorder.

A deficit in P50 sensory gating may be common to BP and schizophrenic patients: the fact that it occurs in euthymic BP cases suggests that it is a marker of vulnerability to psychosis independent of diagnosis.(Sánchez-Moria ea, 2008)

CT studies have shown patients with affective disorders to be similar to schizophrenic patients and significantly different from control subjects in ventricle: brain ratio, sulcal widening, and cerebellar vermian atrophy. Neuroimaging studies in the affective disorders are summarised in the box. Phillips ea (2008) reviewed structural and functional neuroimaging studies of BP patients and found that medication had either no significant effect or ameliorative effects on relevant abnormal structural and functional measures. According to Liddle,(2001, p. 206) structural imaging studies in BP disorder shows focal grey matter loss in the subgenual cingulate gyrus¹³⁰⁴, ventricular enlargement, and deep subcortical white matter hyperintensities. Kempton ea (2008) reported on a meta-analysis of 98 structural imaging studies in BP disorder and found that BP was associated with lateral ventricular enlargement, an excess of deep white matter (but not periventricular) hyperintensities, and, related to lithium use, increased grey matter volume. Importantly, these workers suggest that such studies have appreciable levels of both Type I and II errors. Another meta-analysis of volumetric MRI studies in BP (Arnone ea, 2009) found that patients with this disorder had smaller whole brains and prefrontal lobes as well as larger globi pallidi and lateral ventricles; compared to schizophrenia, BP was associated with smaller lateral ventricles and bigger amygdalae. A number of studies suggested that the closer the lesion is to the frontal pole on the dominant side, and the further away from the pole on the opposite side, the more likely is the person to be depressed. However, Carson ea (2000) found no support for a link between the site of a lesion and risk of depression. A meta-

¹³⁰² NTRK2 gene is the high-affinity receptor gene for BDNF.

¹³⁰³ P85 is an auditory brain potential at 85 ms. Patterson ea (2009) got P50 and P85 from schizoaffective, paranoid schizophrenic (PS), and bipolar I (BP I) subjects. The P85 *gating ratio* (ratio of amplitude of evoked potential at stated number of milliseconds to the first of 2 paired clicks to the response to the second click) was significantly larger in BP I group compared to other groups. P50 gating ratio was significantly larger for schizoaffective group than for controls but failed to distinguish them from PS or BP I. These results need to be replicated.

¹³⁰⁴ However, Hajer ea (2008) found no subgenual volume abnormalities on MRI in unaffected or affected relatives of BP patients suggesting that this is not an endophenotype. These findings are in agreement with those of Hajek ea.(2009) The subgenual cingulate has been stimulated in studies of deep brain stimulation.

analysis of MRI studies in major depression (Koolschijn et al., 2009) showed large volume reductions in frontal regions (especially in anterior cingulate and orbitofrontal cortex – less so in prefrontal cortex) and moderate reductions in hippocampus, putamen and caudate nucleus. The authors point out that the areas affected are involved in emotion processing and regulation of stress. A meta-analysis of five MRI case-controlled studies found reduced area of corpus callosum, with implications for inter-hemispheric integration of information, in BP patients. (Arnone et al., 2008)

Neuroimaging reports in the affective disorders

It should be noted that much of this research involves using affective cases as controls in schizophrenia research.

CT:

Depressive pseudodementia associated with increased ventricle-brain ratio (VBR) and reduced tissue density
Older depressives have similar changes to patients with Alzheimer's disease but not as severe
In CVA, the closer the lesion is to the frontal pole on the dominant (for speech) side, and the further away from the pole on the opposite side, the more likely is the person to be depressed (but see Carson et al., 2000)

MRI:

Increased T1 values in frontal white matter of unipolar (UP) but not bipolar (BP) cases
9 of 19 cases of BP had subcortical hyperintensities (SHI) - SHI associated with more periods in hospital and greater impairment of fluency and recall
Excess deep white matter lesions in first ever late-onset depression
T2-weighted lesions in basal ganglia and pontine reticular formation associated with treatment-refractory depression in elderly
Severe white matter lesions in over 55s associated with worse outlook at mean follow up of 32 months
Subcortical white matter lesions associated with poorer outcome in BP disorder
Young BP patients have increased volume of abnormal white matter not seen with same-aged UP or controls
Enlarged amygdala in hospitalised manics
Enlarged pituitary in depressives (? due to hyperplasia of ACTH-producing corticotrophic cells – trophic effects of CRF)
Enlarged adrenals¹³⁰⁵ **during major depression** (MD) return to normal with remission following treatment
Treatment-resistant chronic UP depressives had reduced grey matter density in L temporal cortex, including hippocampus, with a trend to same on R side; L hippocampal grey correlated with verbal memory
In women with recurrent MD (none with cerebrovascular risk factors) SHI not different from controls
Reduced size of L hippocampus in MD
Smaller hippocampi found in adult women with MD only if they had childhood history of severe/prolonged physical and/or sexual abuse
During Stroop task, BP associated with a trait abnormality in L ventral prefrontal cortex; additional ventral prefrontal abnormalities may be associated with specific acute mood states
Greater progression of white matter hyperintensities associated with poor outcomes in geriatric depression
BP in adolescents and adults associated with decreased volumes of amygdala and hippocampus, esp. the amygdala: suggests early manifestations of BP because of similar findings in both age groups
Homozygosity for the long variant (L allele) of the 5-HT transporter polymorphism is associated with reduced hippocampal volumes in patients with MD but not in healthy controls (this has also been shown for late-onset depression)
Young women with MD have reduced size of hippocampi and larger amygdala volumes compared to controls
Genetic risk for schizophrenia specifically associated with distributed grey matter volume deficits in bilateral fronto-striato-thalamic and left lateral temporal regions; genetic risk for bipolar affective disorder specifically associated with grey matter deficits only in the right anterior cingulate gyrus and ventral striatum; genetic risk for both disorders was associated with reduced volume of white matter in left frontal and temporo-parietal regions; findings interpreted as representing a common fronto-temporal disconnectivity
First MD episode in female cancer survivors after cancer diagnosis does not appear to be associated with hippocampal volume, but longitudinal study with healthy comparison group is needed
Reduced hippocampal volumes found in older (primary MD) depressives (28-82 years of age, mean 53.5, s.d. 13.5); those with either early- or late-onset depression, and those with melancholia showed this phenomenon; such reduction was associated with deficits in visual and verbal memory performance
BP children have reduced grey matter volume in L DLPFC
Poor response to antidepressant treatment of major depression associated with subcortical white matter hyperintensities in L hemisphere but not in other brain areas
Drug-naïve BP patients (but not those who received medication) have shape differences of striatum relative to healthy controls
BP (aged 19-39 years) and controls: in BP, mean temporal volumes reduced and, in some cases, deep white matter lesions present
Medication-naïve BP I associated with smaller corpus callosum

¹³⁰⁵ Presumably due to hypersecretion of ACTH. Such hypertrophy has been found in depressives post mortem and in completed suicides.

Reduced orbitofrontal cortex (OFC) volume occurs in older depressives and is associated with worse lesions of white matter; healthy people with APOE ε4 allele have larger OFC volumes

Regional hippocampal surface contractions were significantly pronounced in late- v early-onset elderly depression in anterior of the subiculum and lateral posterior of the CA1 subfield in the left hemisphere – hippocampal surface contractions correlated with memory measures in late-onset cases only

Elderly depressed subjects differed from elderly non-depressed subjects in having seven regions of white matter hyperintensities despite having equal vascular risk factors

White matter hyperintensities are not associated with vulnerability to psychosis in general, or specifically with affective psychoses

Study of cingulate gyrus grey matter volume: initial and progressive changes in first episode affective psychosis (mainly mania) were confined to subgenual cingulate whereas people with first episode scz had widespread initial and progressively smaller volumes

Reduced amygdala volume in major depression with psychosis but not in major depression without psychosis

Dutch twin study found BP was associated with decrease in total cortical volume; decreases in white matter were related to genetic risk of developing BP; and significant environmental correlations were found for cortical grey matter; and *lithium attenuates the decrease in both grey and white matter*¹³⁰⁶

Carriers of the BDNF Val66Met polymorphism (Val/Met and Met/Met) have relatively small hippocampus, parahippocampal gyrus and amygdala

Diffusion tensor imaging (DTI) revealed decreased size of anterior cingulum in BP

First-episode MD (n = 28 in-patients) – significant negative correlation between major life events 3 months before onset of depression and left hippocampal volume in males; no significant association found for females

DTI in BP showed greater white matter fractional anisotropy in the left orbitomedial PFC that decreased with age and with alcohol/drug misuse, as well as reduced white matter fractional anisotropy in the right orbitomedial PFC

Major depression associated with decline in grey matter density of hippocampus, anterior cingulum, left amygdala, and right dorsomedial PFC – remission during 3-year study was associated with lesser changes

DTI showed similar white matter abnormalities in BP and schizophrenia

Treatment-resistant UP and BP depressives showed reduced global cortical folding and lithium may modify cortical folding in BP cases; limitations include overlap with normal controls and inability to distinguish trait and state effects

Looked at type II diabetes (DMII) + depression, DMII without depression, and healthy controls: magnetization ratios significantly lower bilaterally in caudate head in type II diabetes (DMII) + depression group; non-depressed DMII had intermediate values

Looked at anterior cingulate cortex in patients with first psychotic episode in BP-I – males had thicker right subcallosal limbic anterior cingulate cortex that was not explained by medication effects; no differences between female patients and healthy controls (should the patients have compared with BP-I without psychosis?)

Grey matter deficits in inferior frontal regions in patients (N = 56) with mean age of 60.5 years

DTI performed on psychotic BP I cases, unaffected first-degree relatives, and controls: patients had decreased fractional anisotropy in genu of corpus callosum, right inferior longitudinal fasciculus, and left superior longitudinal fasciculus; patients and their relatives had decreased fractional anisotropy across distributed regions of white matter – the structural integrity of key intra- and inter-hemispheric tracts was disturbed in BP and unaffected relatives

Compared to matched controls, DSM-IV BP adults (mean age 60.5 years) had significantly smaller gray matter volumes bilaterally in inferior frontal areas (part of the anterior limbic network)

Amygdala volume of euthymic BP I patients receiving lithium was larger than that of healthy controls whereas amygdala volume of euthymic BP I patients not receiving lithium was similar to that of healthy controls

DTI found ‘early’ changes in course of BP (i.e. patients were adolescent) in areas associated with regulation of emotion, behaviour, and cognition (lower fractional anisotropy in fornix, left mid-posterior cingulate gyrus, all of corpus callosum, fornico-thalamic fibres, and parietal and occipital corona radiata bilaterally)

Healthy people show an inverse relationship between impulsivity and orbitofrontal cortex volume; however, impulsivity may have a different neural representation in BP wherein the anterior cingulate cortex may be implicated

Currently euthymic BP and controls: generalised white matter microstructural abnormalities in BP; these may have been exacerbated by past drug abuse and lessened by lithium

In Women’s Health Initiative Memory Study abnormal white matter lesions related to hypertension in most brain areas and are greatest in frontal lobe than in other lobes; baseline blood pressure level strongly related to white matter lesion volumes

White matter hyperintensities (rather than cortisol levels or cerebral atrophy) are associated with continuing cognitive impairment in depressed older adults

Baseline severity of white matter changes in older subjects independently predicted depressive symptoms at both 2 and 3 years and white matter changes predicted incident depression

Late-onset MD may be associated more with white matter lesions in areas important for cognition and emotion (left superior longitudinal fasciculus and right frontal projections of corpus callosum) than with total lesion load; lesion load correlated highly with smoking

fMRI:

Children and adolescents with familial BP may have abnormal regulation of prefrontal-subcortical circuits

Antidepressant treatment of MD reduces L limbic, subcortical, and neocortical capacity for activation and increases the dynamic range of the L prefrontal cortex in patients shown sad faces

¹³⁰⁶ See van der Schot et al (2009).

A common regulatory variant (5-HTTLPR) in human 5-HT transporter gene (SLC6A4) has a strong modulatory effect on amygdala reactivity to environmental threat, and might represent a susceptibility for affective disorders

Controlled study of juvenile of parents with history of MD showed greater amygdala and nucleus accumbens activation to fear faces and the opposite response to happy faces – these results held true for passive viewing but not for constrained (told to look at the nose only) attention, the latter probably recruiting medial prefrontal cortex to a greater degree

MD, relative to controls, associated with increased response time from neutral to sad words on emotional Stroop task and significant engagement of left rostral anterior cingulate cortex and right precuneus during sad words

Lamotrigine might enhance facial affect recognition in bipolar disorder

BP show abnormal fronto-striatal activity when performing a set shifting task, perhaps excessively engaging emotional brain areas

Whilst controls activated the pregenual anterior cingulate cortex in response to positive and negative words during emotional Stroop task, young people with depressed parents did not activate this area

Men with histories of attempted suicide show different pattern of brain activation in response to angry faces compared to non-suicidal comparison subjects

In MD there is abnormal connectivity of dissociable prefrontal and cingulate regions – increased connectivity of dorsolateral prefrontal cortex during task-induced activation and increased connectivity of anterior cingulate cortex during task-induced deactivation

MD shows weak response in left nucleus accumbens and both caudate nuclei during monetary incentive delay task

In the elderly, during a test that activates lateral prefrontal cortex-anterior cingulate cortex (ACC), anxious depressives seem to expend greater and more sustained effort (involving the ACC) than do depressives

Measuring BOLD signals, authors found that abnormal amygdala-prefrontal effective connectivity to happy faces distinguished BP depressed patients from MD depressed patients

In BP there is relatively greater increases in activation for emotional v neutral scenes in left hippocampus than is seen in healthy controls or schizophrenia patients; there is a positive correlation between mania scores and activation in ACC, and a significant negative correlation between depressive scores and DLPFC activation

PET:

Severely depressed UP and BP had significant L-R prefrontal asymmetry before but not after successful TCA treatment (? state); significant hypofrontality and whole cortex hypometabolism in depressed and treated states (trait?)

5-HT₂ receptor study with [¹⁸F] altanserin – uptake reduced in drug-free UP in R (trend for L to be similarly affected) posterolateral orbitofrontal cortex and anterior insular cortex

Brain 5-HT₂ receptors decreased in MD

Men recovered from depression subjected to tryptophan depletion had reduced neural activity in ventral anterior cingulate, orbitofrontal cortex, and caudate, as well as attenuated cognitive task-related activation in anterior cingulate cortex (small numbers of males on antidepressants)

Healthy women before and after rapid tryptophan depletion: decrease in plasma free tryptophan levels but no effect on mood; decreased cortical 5-HT₂ receptor binding (which may be protective against depression)

Increased anterior paralimbic activation from waking to REM may be related to depressed mood, whereas increased activation of executive cortex may be related to cognitive dysregulation in depressed patients

Magnitude of regional 5-HTT binding potential can provide a vulnerability to low levels of extracellular 5-HT and very negative dysfunctional attitudes

DSM-IV BP manic episode and healthy controls: evidence suggests decreased 5-HT₂ receptors in acute mania

SPECT:

rCBF lower in orbital frontal and anterior temporal regions (especially on R side) in medication-free older physically healthy depressed

Greater degree of depression in UP with diurnal mood variation associated with increased cingulate and other paralimbic perfusion

DA transporter affinity may be increased in basal ganglia in major depression

Patients over 55 years of age with depression (HAM-D) given average of 13.7 weeks antidepressant treatment showed improvement in rCBF in left DLPFC to precentral region (? Represents functional/reversible problem) whereas no real improvement in bilateral medial/dorsolateral/parietal (? Trait-dependent)

MRS:

Decreased GABA in occipital cortex in MD

Myo-inositol/creatinine and choline/creatinine ratios increased in frontal white (but not gray) matter in (major) depressed elderly

Euthymic males with familial BP I: lower levels of N-acetylaspartate and creatinine but normal choline levels in R and L hippocampi; significant negative correlation between N-acetylaspartate concentration in R hippocampus and illness duration

Replication of finding of reduced GABA level in occipital cortex in MD; also, mean glutamate levels decreased in depression; and, decreased solid tissue and the percentage of white matter in the voxel

Young and adult BP patients have decreased N-acetylaspartate (NAA) levels in DLPFC (? underdeveloped dendritic branching and synaptic connections)

Adolescents with MD have increased choline and creatinine in left caudate, likely due to rapid membrane turnover and impaired metabolism

Increased choline-containing compounds (glycerophosphocholine and phosphocholine) in orbitofrontal cortex and hippocampus in euthymic BP patients; since choline is a marker for membrane phospholipid metabolism the increased levels may mean increased membrane breakdown, i.e. cell loss

A low 5-HT level might prime the brain so that if now catecholamine levels rise the person becomes manic, but should they fall depression ensues. Thakore et al (1996) suggest that the finding of blunted d-enfluramine-

induced prolactin release in bipolar mania supports the notion that both BP and UP affective disorder are associated with decreased serotonergic responsivity.

It has been said that intracellular sodium rises in depression, and rises still further in mania. Vanadium poisoning of the sodium pump was a popular suggestion as a cause of affective disturbance during the 1980s, patients being subjected to massive doses of ascorbic acid as a putative antidote.

Many drugs can cause depression (e.g. steroids¹³⁰⁷, alpha-methyl dopa, beta-blockers that cross the blood brain barrier¹³⁰⁸, cimetidine, reserpine, tetrabenazine, vigabatrin (Sabril – up to one third of patients develop visual field defects), and BZDs (do they cause or unmask it?: Tiller & Schweitzer, 1992), or stimulant withdrawal), or have a depressive aftermath (e.g. amphetamines). Isotretinoin (Isotrex, Isotrexin, Roaccutane), a vitamin A derivative used for severe acne, has been blamed for depression, psychosis and suicide. Whilst great care is required to monitor for depression in cases treated with isotretinoin, it should be recalled that acne itself is commonly associated with depression (Anonymous, 2003) and the literature is far from unanimous in its findings re isotretinoin. (Jick ea, 2000; Magin ea, 2005) Isotretinoin should be prescribed by a dermatologist for severe, refractory acne and it should either be stopped if depression occurs or psychiatric assistance should be enlisted. There has been a report of a florid hallucinatory and delusional state complicating TCA treatment of steroid-related depression. (Hall ea, 1978) The most common depressogenic agent is alcohol, either as an adjustment disorder or a direct effect of alcohol on mood. Certainly, comorbid alcohol use disorder, common in BP, increases suicidal behaviour beyond that associated with non-comorbid BP. (Oquendo ea, 2010) L-DOPA can cause depression or hypomania. It can also cause confusion/delirium, agitated restlessness, psychosis, and, less commonly, hypersexuality. Depression and physical deterioration are associated with lack of activity. There seems to be an increased risk of coronary artery disease in depressives¹³⁰⁹. Bone mineral density (spine and hip) has been found to be lower in depressives than in controls, especially in females. (Wu ea, 2009) Depression may be secondary to such physical disorders¹³¹⁰ as Addison's disease, Parkinson's disease¹³¹¹, heart failure¹³¹², myocardial infarction, stroke¹³¹³, chronic pulmonary disease, hip fracture, and bronchogenic or pancreatic carcinoma. Presumed intrauterine (second trimester) starvation in males during a Dutch famine has been found to correlate with later affective psychosis, but not with neurotic depression. (Brown ea, 1995) A report of an association of poor weight gain in infancy and adult suicide may reflect the operation of psychosocial or biological factors. Similar considerations probably apply to the Swedish findings of Mittendorfer-Rutz ea (2004) who reported that multiparity and low maternal education predicted suicide attempt in offspring, whereas as restricted foetal growth and teenage motherhood were associated with both completed suicide and attempted suicide in the offspring. Both B12 and folate deficiency may be associated with depression, although they are not always primary. Mania has been reported to occur secondary to many conditions. (see box) Many reports are anecdotal and it is often difficult to make a strong case for direct causation. There is no good evidence to link affective psychosis or mania to problems at birth. DSM-IV does not allow manic-like episodes clearly secondary to antidepressant treatment¹³¹⁴ to count toward a diagnosis of BP I disorder. Overactivity, pressured speech, and racing thoughts during bipolar depression should alert the therapist to enhanced risk for conversion to mania with antidepressant drugs. (Frye ea, 2009)

¹³⁰⁷ Corticosteroids change sensitivity of noradrenergic receptors by regulating the brain's beta-adrenoreceptor-coupled adenylate cyclase system; antidepressants activate the cAMP cascade causing BDNF and CREB release leading to hippocampal neurogenesis.

¹³⁰⁸ Beta-blockers, however, may not be as depressogenic as they are normally stated to be. (Long & Kathol, 1993; Ko ea, 2002)

¹³⁰⁹ Not totally attributable to other risk factors such as tobacco.

¹³¹⁰ Farmer ea (2008) found that people with recurrent depression were more obese than controls and had an excess of gastric ulcer, rhinitis/hay fever, osteoarthritis, thyroid disease, hypertension and asthma.

¹³¹¹ Based on SPECT findings, major depression in Parkinson's disease may be a consequence of advanced and widespread neurodegeneration. (Pålhagen ea, 2009)

¹³¹² Heart failure leads to depression and treatment of heart failure with loop diuretics reduces the risk of depression as shown in a Dutch population-based study of elderly subjects. (Luijendijk ea, 2010)

¹³¹³ Depression is associated with increased mortality post-CVA. Stroke cases are more depressed than 'similarly disabled' orthopaedic patients. The 5-HTTLPR and the STin2 VNTR polymorphisms of the 5-HT transporter gene may be associated with post-stroke depression. (Kohen ea, 2008) SSRI drugs tend to be prescribed, although nortriptyline was superior to fluoxetine in one small study of post-CVA depression. (Robinson ea, 2000)

¹³¹⁴ E.g. antidepressant drugs, ECT or light therapy.

Possible causes of secondary mania¹³¹⁵

Delirium
 ECT
 Huntington's, Wilson's, and Pick's diseases
 Kleine-Levin and Klinefelter's syndromes
 Post-encephalitic Parkinsonism, GPI, viral encephalitis, HIV
 Cerebral tumours or trauma (e.g. closed temporal basal polar injury, diencephalic glioma, suprasellar craniopharyngioma, tumour of floor of fourth ventricle, metastatic deposits in right temporo-parieto-occipital area, right-sided intraventricular meningioma)
 Cerebrovascular accident¹³¹⁶ (CVA)
 MS
 Thalamotomy
 Right temporal lobectomy
 TLE
 Open-heart surgery
 Carcinoid syndrome/serotonin syndrome
 Uraemia, haemodialysis, dialysis dementia
 Hyperthyroidism
 Hypoadrenalism, Cushing's disease
 B12 deficiency, pellagra
 Postpartum¹³¹⁷
 Post-isolation syndrome
 Drugs (those reported): metoclopramide, L-DOPA, baclofen, cimetidine, cyclobenzaprine, bromocriptine, sympathomimetics, bronchodilators, decongestants, corticosteroids, ACTH, disulfiram, hydralazine, INAH, dapsone, metrizamide (myelography), procarbazine, procyclidine, bromides, barbiturates, anticonvulsants, benzodiazepines, antidepressants, yohimbine, stavudine (d4T), zidovudine (AZT), didanosine, efavirenz, calcium replacement, hallucinogens, cocaine, amphetamines, PCP

Immunological findings in depression have included an impaired lymphocyte response. There are an increased number of circulating neutrophils and a fall in NK (natural killer) cells, T and B lymphocytes, and helper and suppressor/cytotoxic T cells. There are also a reduction in NK cell activity and lympho-proliferative responses to mitogen stimulation. B cell function is also affected. Resolution of major depression in HIV-positive women is associated with increased NK cell activity. (Cruess ea, 2005)
 Depressed patients have increased antibody titres to herpes simplex virus (HSV-1) and cytomegalovirus compared to other hospitalised or healthy groups. A greater number of depressives respond to in vitro stimulation with HSV during the acute phase of their illness than during a remission. Ader ea (1995) wondered if there might be a latent herpes infection that becomes reactivated during depression. The finding of an increase in soluble receptors for interleukin-2 receptors in the plasma of suicide attempters might indicate either a state or trait marker.

Genetics

Genetic factors are often thought to be important in severe cases of depression and in cases with somatic symptoms whereas environmental factors may appear to be more important in milder cases of depression. Also, single genetic abnormalities can only explain a small part of all mood disorders. (Baldwin & Hirschfeld, 2005, p. 25) However, the interaction between genes and environment is complicated, e.g. while sensitivity to stress in adulthood may be due to sensitisation as a result of exposure to earlier stressors genes associated with depression may speed up the process of stress-induced sensitisation. (Wichers ea, 2009a, b) El Hage ea (2009), discussing vulnerability to depression, suggest that gene-environment interaction involves complicated involvement of serotonergic genes that modulate responses to stress via the hypothalamico-pituitary-adrenal system.

¹³¹⁵ Referred to as 'disinhibition syndrome' by neurologists, it is often associated with cognitive dysfunction.

¹³¹⁶ Perhaps particularly associated with right-sided vascular lesions.

¹³¹⁷ Sharma ea (2008) looked at 56 consecutive females referred with a diagnosis of postpartum depression and made the following primary DSM-IV Axis I diagnoses: major depressive disorder (46% of cases), bipolar disorder (BPD) not otherwise specified (29%), BPD II (23%), and BPD I (2%). They suggest that misdiagnosis of bipolarity may be common in such cases. Sharma ea (2009) suggest that hypomania after delivery is common and often misdiagnosed; also, bipolar II depression is often misdiagnosed as unipolar major depression and may be inappropriately treated with antidepressants.

The first degree relatives of UP probands have an increased rate of UP. The same relatives of BP probands have increased rates of UP and BP, especially UP. Cyclothymic mood swings may be found in a quarter of adolescent offspring of BP parents¹³¹⁸. Research is complicated by the fact that a number of apparently UP cases have had missed hypomanic episodes or haven't yet had a manic attack, i.e. they are truly BP!

Behavioural disinhibition (extreme tendency to seek novelty, approach the unfamiliar, and display disinhibited speech and action in unfamiliar settings) is increased in offspring of BP parents.(Hirshfeld-Becker ea, 2006) Indeed, impulsivity may be a 'core' feature of BP regardless of illness phase.(Swann ea, 2008)

Twin studies of BP disorder have yielded results similar to those for schizophrenia. Concordance rates for MZ twins (40-60%) are much higher than those for DZ twins. The risk of BP in offspring of MZ twins discordant for BP is the same whether the parent (twin) did or did not develop BP!(Jones ea, 2002)

Major affective disorder has been described in a family in association with the rare autosomal dominantly inherited keratosis follicularis¹³¹⁹. The association of consanguinity and puerperal psychosis in three British sisters suggests a single major susceptibility locus of recessive effect. But these are rare phenomena. Twin studies of major depression suggests that this is an artificial category consisting of depression symptoms of varying severity and duration.(Kendler & Gardner, 1998)

A major Swedish study suggests that schizophrenia and bipolar disorder are genetically overlapping disorder.(Lichtenstein ea, 2009)

Affective disorders: highlights of chromosomal research

Chromosome	Comments
1	?gene or genes predispose some to depression and some to alcoholism; perhaps the depression is alcohol-induced; DISC1 (1q42.1) and BP; 1q21.3-q.32.1 for 'postpartum mood symptoms'
2	Suggestive overlap of bipolar disorder (BP) with schizophrenia at 2p11-q14, e.g. MAL (2cen-q13); CREB1 (cAMP-responsive element binding protein 1 at 2q34 and important in cAMP signalling) and major depressive disorder (MDD)
3	Somatostatin (SST, 3q28, involved in GABA signalling) and BP
4	E.g. D5 dopamine receptor and adrenergic 2C receptor genes; FGF2 (fibroblast growth factor 2 at 4q26-q27 with neuroprotective role); FAT (FAT tumour suppressor homologue 1, 4q34-q35, with adhesion and signalling functions) and BP
5	Possible linkage between locus near the dominant DA transporter and BP disorder
6	Discrepant findings in relation to HLA region; dysbindin polymorphisms may increase susceptibility to BP I; HEY2 (hairy/enhancer-of-split related YRPW motif 2, 6q22, involved in neurogenesis and transcription) and BP
8	Neuregulin-1 may influence susceptibility to schizophrenia and BP disorder; 8p and MDD; possible connection between 8q24 and puerperal bipolar affective psychosis
9	9p24.3-p22.3 for 'postpartum mood symptoms'
11	No evidence between mutations on q arm and manic depression in 5 Icelandic pedigrees Belgian linkage study fails to find linkage between BP and p15 (such a linkage had been found initially in Old Order Amish but did not replicate with bigger group) BDNF (11p13-p12) and BP; SLC1A2 (glial high-affinity glutamate transporter 2 at 11p13-p12 with glutamate removal role)
12	Darrier's disease (12q) cosegregated with BP in two pedigrees ¹³²⁰
13	D-amino acid oxidase activator (DAOA)/G30 locus (formerly G72/G30) may be associated with schizophrenia, major depression, neuroticism, and BP (espc. with persecutory delusions). Overlap of BP with schizophrenia at 13q21-33. DGKH (diacylglycerol kinase eta, 13q14.11) gene codes for an important enzyme in the lithium-sensitive phosphatidyl inositol pathway
15	15q and MDD
16	16p 13 and bipolar affective puerperal psychosis ¹³²¹
17	SLC6A4 (5-HT transporter, 17q11.1-q12)
18	Possible susceptibility gene near centromere in BP disorder; not all studies agree
19	Possible shared susceptibility locus on 19q13 (MAG or myelin-associated glycoprotein at 19q13.1) between BP and schizophrenia in familial cases
20	Discrepant findings
21	TRPM2 (transient receptor potential cation channel M2 at 21q22.3, involved in calcium homeostasis)

¹³¹⁸ Regeer ea (2004) reported cyclothymia in 4.2% of the Dutch general population.

¹³¹⁹ **Darrier's disease:** skin disorder, epilepsy, intellectual disability, with gene at 12q23-24.1.

¹³²⁰ Whilst the gene for Darrier's disease has been identified as ATP2A2, mutations at this gene have not been reported in patients with BP disorder.(see Green ea, 2005) There are reports implicating 12q24 with BP.(Kalsi ea, 2006)

¹³²¹ See Jones ea (2007)

22	Velo-cardio-facial syndrome patients may have excess relatives with BP disorder ¹³²² with early onset; COMT (22q11.2) and BP; ADRBK2 (GRK3) or G-protein coupled receptor kinase 3 (22q11.13-22q12.1, involved in GPR signalling) and BP; APOL or apolipoprotein gene cluster (22q13) and BP
X	No evidence of linkage with BP

Caspi ea's (2003), Kendler ea's (2005) and Otte ea's (2007) work suggests that individuals with 2 short alleles (SS) at the 5-HTT locus¹³²³ have increased sensitivity to mild stressors. While the short allele of the 5-HTT gene may increase vulnerability to mood disorders it may also have a role to play in social phobia/social anxiety disorder (Furmark ea, 2004) and PTSD.(Lee ea, 2005)

There is evidence of widespread dysregulation of mitochondrial energy metabolism and downstream deficits of ATP-dependent processes in BP.(Konradi ea, 2004) This is associated with reduced expression of *nuclear* mRNA coding for mitochondrial proteins in BP subjects.

Genetic liability to depression is in part expressed by a tendency to negative affect in response to minor daily tribulations.(Wichers ea, 2007)

A developmental twin study of anxiety and depression symptoms (Kendler ea, 2008a) suggests that different genetic risk factors switch on and attenuate later at different ages.

A genome-wide association analysis (Ferreira ea, 2008) supported a role for the genes ANK3 and CACNA1C¹³²⁴ (12p13.3; encoding for the alpha subunit of the calcium channel Ca_v1.2)¹³²⁵ with increased risk of BP. Both play a role in ion channels in nerve cells and affect neuronal excitability levels: ANK3, which which encodes the protein ankyrin G, is involed in sodium channel regulation, whilst CACNA1C is involved in calcium channel regulation. Could BP result from multiple rare structural variants? A polymorphism (rs1006737) within CACNA1C may confer risk for BP, recurrent MDD, and for schizophrenia.(Green ea, 2009) A genome-wide copy number variant (CNV) survey (Zhang ea, 2008) found that singleton deletions¹³²⁶ more than 100 kb in length were present in 16.2% of BP cases and 12.3% of controls (p=0.007), an effect that was more pronounced for age at onset of mania under 18 years. However, CNVs may be associated more with schizophrenia than with BP.(Grozeva ea, 2010)

Conditions included among affective (mood) disorders

Various depressive syndromes have often been noted to fail to remain stable on follow up.(Young ea, 1990) It is necessary to briefly discuss some of the forerunners of present day nosologies because they still appear in the literature,(van Praag, 2001) are of historical importance, and still appear under different names, and because today's taxonomies are imperfect.

The presence of a precipitant does not decide if a condition is endogenous or exogenous in origin. Mixtures of endogenous and exogenous depression are more common than either is in pure form.(Kendell, 1993) Andreasen ea (1986) found no difference in the rates of depressive illness between the relatives of patients with endogenous versus non-endogenous depression. Psychotic and endogenous are not synonymous. In some cases (atypical, masked, smiling [putting on a brave face], depressive equivalents) affective change is not prominent, although the concept of 'depression without depression'¹³²⁷ has been attacked by Stefanis and Stefanis.(1999) Such cases may present in the form of psychosomatic disorders, pains - such as atypical facial pain¹³²⁸, hysterical conversion syndromes, and hypochondriasis. In fact, according to Paykel (1989), the term atypical depression has three different meanings: marked anxiety and phobic symptoms; reversed functional shift (worse in evenings¹³²⁹); and non-endogenous depression in general. Other suggested guises include depressive pseudodementia (*vide infra*), alcohol abuse¹³³⁰, shoplifting, sexual

¹³²² A high incidence of BP I and II and cyclothymia was noted in patients with velo-cardio-facial syndrome by Papolos ea.(1996)

¹³²³ These alleles involve the promoter region of the 5-HT transporter gene, the latter being involved in serotonin reuptake by cell membranes.

¹³²⁴ **Timothy syndrome** is a rare autosomal dominant disorder with cardiac, digital and facial problems. Autism or autistic spectrum disorder may be found in those who live long enough. Mutations occur in the CACNA1C gene.

¹³²⁵ Drugs acting on this channel might be effective in BP, e.g. verapamil, diltiazem, nimodipine, and flunarizine.(Keers ea, 2009)

¹³²⁶ These are deletions that appear only once in the dataset.

¹³²⁷ *Depressio sine depressione*.

¹³²⁸ Intense, continuous pain; distribution may transcend V nerve boundaries; may have subjective facial swelling.

¹³²⁹ Concept introduced by English psychiatrist John Deryk Pollitt (1926-2005) in 1960.

¹³³⁰ According to Farren (2008) the adjusted odds ratio for comorbid alcohol dependence is 4.6 for BP I disorder and 3.0 for BP II disorder. He also suggests that cognitive therapy and sodium divalproex may be helpful in such cases.

disinhibition, ego-dystonic temper outbursts, behaviour disorder in the elderly¹³³¹, jealousy, new-onset loneliness¹³³², an anxiety state, accentuated personality traits, or an abnormal grief reaction. Increased appetite (craving for high calorie foods), heightened rejection sensitivity, and leaden paralysis ('heavy' feeling in limbs – like wading through water) are atypical features of depression. According to Kelsey ea, (2006, p. 162) atypical depression is characterised by chronic sensitivity to interpersonal rejection with relationship difficulties and overreaction to perceived slights. Sims (2003, p. 314) suggests that smiling depressives may be consciously concealing their low mood from habit of masking emotions or from an attempt to avoid treatment. Mixed states¹³³³ of different affects may occur, e.g. up to 40% of bipolar patients have mixed episodes at some time.(Calabrese ea, 1996) In dysphoric mania,¹³³⁴ mania is said to be present when the criteria for both major depression and mania are met simultaneously – many manic admissions fulfil criteria for mixed states. Bipolar I and II depressions are often accompanied by manic symptoms that may be missed because they are subtle or because they are overshadowed by the depression.(Goldberg ea, 2009) Kraepelin described 6 types of mixed affective state during the early 1920s: depressive/anxious mania, excited depression, mania with poverty of thought, manic stupor, depression with flight of ideas, and inhibited mania.

Pain is common in depression (von Knorring, 1975) and may be the sole symptom.(Simon ea, 1999) Suggested forms of depressive equivalents include sociopathy and alcoholism in male relatives, the same in the index patients, illegal drug abuse, psychocutaneous syndromes, peptic ulcers, and, in children, disorders such as autism, insomnia, theft, gastrointestinal upset, encopresis and school phobia.

Many depressed patients only have physical complaints without a known biological cause; others have symptoms disproportionate to medical findings. Doctors may collude with patients in avoiding discussion of psychosocial factors. Overt depressed mood is less common as a symptom in ethnic minorities and elderly subjects than in the average depressive.

One classification of affective disorders is into *primary* (arising independently) and *secondary* (e.g. due to carcinoma). *Personal depression* infers that the patient can see a connection between his life circumstances and his mood disturbance. In the absence of such a connection the term *vital depression* has been employed.

Another classification of depression was into *pure depressive disease*, especially affecting older men; whose relatives of both sexes showed an equal prevalence of depression, and *depression spectrum disease* affecting mainly young females whose relatives showed a greater prevalence of depression among females, their male relatives tending to be alcoholics or psychopaths. A more modern meaning of depressive spectrum¹³³⁵ disorders is one inclusive of major and minor depression and dysthymia.(Hermens ea, 2004) Depending on the particular nosology, unipolar might mean attacks of depression only, or of depression or mania only, and bipolar may denote attacks of depression and mania or of mania only. Perhaps 5-10% of patients experiencing an episode will develop mania in the future.(Lam & Mok, 2008, p. 31) The RDC distinguish between bipolar I disorder, wherein mania has occurred, and bipolar II disorder¹³³⁶, when only hypomania has been recorded. Some two-thirds to three-quarters of patients admitted with manic illness will suffer at least one relapse requiring hospital admission. This may not take into account missed mild attacks. Hypomania is simply a mild form of mania and is the commoner form seen today. About 5% to 15% of people with hypomania will develop mania some time in the future. DSM-IV-TR defines hypomania as not being severe enough to markedly impair social or occupational functioning, not necessitating hospitalisation, and being non-psychotic, a most unhelpful definition because of variations in

¹³³¹ E.g. the elderly nursing home resident who screams, lashes out, and voids anywhere but the toilet.

¹³³² E.g. an older person requesting re-housing.

¹³³³ **Mixed affective episode:** According to DSM-IV-TR the criteria are met for a manic episode and a major depressive episode nearly every day for a one-week period. ICD-10 requires at least 2 weeks of a mixture that can include extremely fast changes (hours) between 'highs' and 'lows'. Should manic stupor - the smiling but motionless patient - be included under this heading or should it be seen as mania complicated by stupor?

¹³³⁴ Described by Clothier and colleagues in the 1990s. It may be more common in females, carry an increased suicide risk, have a relatively poor outlook, and be comparatively lithium-resistant.

¹³³⁵ Or absence of clear boundaries.(Widiger & Mullins-Sweatt, 2007, p. 7)

¹³³⁶ This distinction between **two types of BP** became official in DSM-IV. The concept of bipolar II disorder is controversial because we do not have an empirically validated, sensitive definition of hypomania.(Angst, 2007) However, there are follow up and family studies that favour the distinction between the two types of bipolar disorders.(Benazzi, 2007) 10% of BP II disorders convert to BP I disorder over 10 years by having a manic or mixed episode.(Coryell ea, 1995) Importantly, BP II disorder is not necessarily less disabling than BP I disorder.(Baldessarini ea, 2000)

demands on patients, local admission (and insurance) policies, and the fact that full mania is not necessarily accompanied by hallucinations or delusions.

Abbreviated DSM-IV-TR criteria

Bipolar I disorder

Current/most recent episode was manic

In past there was at least 1 major depressive, manic, or mixed affective episode

Current/most recent episode not due to schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified

Bipolar II disorder

Present/history of at least one major depressive episode

Present/history of at least one hypomanic episode

No history of manic or mixed affective episodes

Not due to schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified

Symptoms cause clinically significant distress/impairment in important areas of function, e.g. social

Klerman's (1987) classification of BP disorder included six types (I-VI)!

Reactive depression infers the presence of an intrapsychic or environmental precipitant. Sometimes 'reactive' was used as synonym for 'neurotic'.

Neurotic depression was said to typically afflict the young adult who is under stress. It represented an exaggeration of normal unhappiness. The mood varies and distraction gives some relief. There is no consistent diurnal (over 24 hours) rhythm, or the mood may get worse towards evening. Initial insomnia may occur, the sufferer finding it hard to drop off to sleep. The patient projects the responsibility for their problems onto other people or things.

Endogenous depression was said to be most common in middle age. A family history was usual and the premorbid personality is often socially well adjusted. It was held that life events leading up to the breakdown, such as moving house or redundancy, were reported as having been excessive over a period of months. The mood is qualitatively different to unhappiness, the patient may be agitated¹³³⁷ or stuporose and the patient might hear voices saying something like 'You are a sinner'. Common symptoms included hypochondriasis, guilt¹³³⁸ feelings, and even delusions of worthlessness. Intellectual capacity is particularly dulled in severe¹³³⁹ depression. The patient demonstrated retrospective falsification, with no good memories. Early morning wakening (EMW or terminal insomnia), loss of appetite and weight, amenorrhoea, loss of libido, constipation, and a lightening of depression as the day goes on, are common. Obsessional symptoms could be exacerbated or arise de novo.

Whilst both DSM-IV and ICD-10 state that mood in major depressive disorder (MDD) is usually worse in the morning the lowest point in mood may be at any point in the day in practice, and an evening low point, although classically associated with anxious/neurotic/reactive/atypical cases, can also occur in melancholic/endogenous depression.(e.g. Morris ea, 2007)

Involuntional melancholia referred to an older patient with neurotic and endogenous depressive features. It is no longer considered as an entity. The family history of such patients shows an increased frequency of affective disorder, not often involuntional. Hypochondriasis was the hallmark of this once-popular syndrome.

¹³³⁷ Agitation is not an all or nothing phenomenon and can be episodic, alternating with psychomotor retardation.

¹³³⁸ Guilty feelings are particularly prominent in Western depressives. Shame or humiliation may be the main complaint in some other parts of the world. Comedians who are depressed may become adept at using irony: self-deprecation as a symptom of depression may be missed under such circumstances.

¹³³⁹ There is no generally accepted **definition of severe depression**. Candidates include rating scales with cut-off scores (open to inter-rater variation), hospitalisation (resource and policy driven), suicidal thinking (role of alcohol, personality, exit events, etc – and may occur in mild depression), chronicity (not synonymous with severity), melancholic subtype (ditto), resistance to treatment (ditto), and interference with function (many other factors interact with depression severity to cause dysfunction, e.g. coping style, social expectations, and cultural practices).

A classification of depression dating from the 1960s included *type S depression* on the one hand (functional shift¹³⁴⁰) and *type J depression* (justified depression). These closely resemble endogenous and reactive depressions.

Parker (1978) divided reactive depression into under- and over-bonded types. The *underbonded* depressive experienced some degree of rejection by parents during formative years while the *overbonded* subject was over protected by parents and did not become emotionally independent of them. He subdivided underbonded depression into stunted self-esteem¹³⁴¹, sensitised self-esteem¹³⁴², and mixed forms of the above. In the overbonded patient at least one parent has been overprotective, the second parent may be absent, submissive, or also over protective, and the patient often gets depressed for the first time when he leaves home.

Leonhard described the so-called *cycloid psychoses* in 1957. They were all bipolar disorders, of good prognosis, led to no chronic defect state, and yet were difficult to distinguish from schizophrenia.¹³⁴³

The main classifications are those of ICD-10 and DSM-IV.

Modern classifications of the affective disorders

(a) ICD-10 (F30-39)

F30 Manic episode is divided into hypomania, mania with/without psychotic symptoms, other manic episodes, and unspecified manic episode.

F31 Bipolar affective disorder (at least 2 affective episodes of which 1 must be manic, hypomanic or mixed) asks if the current episode is hypomania, mania (with/without psychotic symptoms), depression (mild/moderate/severe, with/without somatic or psychotic symptoms), mixed (hypomanic/manic/depressive symptoms experienced together or rapidly alternating), other or unspecified.

F32 Depressive episode may be mild/moderate/severe (the first 2 with/without somatic symptoms, the last with/without psychotic symptoms), other (included atypical depression) or unspecified.

F33 Recurrent depressive disorder – the current episode may be mild/moderate/severe (the first 2 with/without somatic symptoms, the last with/without psychotic symptoms), other or unspecified, or the patient may be in remission.

F34 Persistent mood (affective) disorder may be classified as cyclothymia,* dysthymia,** other or unspecified.

F38 Other mood (affective) disorders may be classified as a single episode (state if mixed) or recurrent (state if brief depressive), or other.

F39 Unspecified (a last resort category).

*A persistent instability of mood, involving numerous periods of mild depression and mild elation, usually starting early in adult life, often pursuing a chronic course, remissions are possible, and the patient usually does not relate it to life events. It includes 'affective personality disorder', 'cycloid personality' and 'cyclothymic personality'. The term 'dysthymia' has been attacked as medicalising despair.

**A chronic depression of mood not filling criteria for even mild recurrent depressive disorder in terms of either severity or duration of individual episodes, although the patient may have started off with a mild depressive episode or suffered one at some other stage. It includes 'depressive neurosis', 'depressive personality disorder', 'neurotic depression' with over 2 years' duration, and 'persistent anxiety depression'. According to Michels and Marzuk (1993), 'The boundaries between dysthymia, chronic unremitting major depression, and depressive personality traits remain controversial.' Another view is that dysthymic disorder is a disorder of mood with greater mood fluctuations than in depressive personality disorder. The latter is chronic and lifelong, whereas the former is episodic, can occur at any time, and usually has a precipitating stressor.

(b) DSM-IV

¹³⁴⁰ E.g. early morning waking or EMW, diurnal mood changes where the patient feels worse in the morning, etc.

¹³⁴¹ Preoccupied with not offending others, afraid of incurring criticism, made the object of parental anger or criticism in early childhood, one parent may be absent or passive.

¹³⁴² Feels normal in between bouts of depression, ceases to function well under stress, e.g. when jilted, finds it hard to trust others, and parents may have been emotionally distant and only responsive when he achieved something such as when passing an exam or on being promoted at work.

¹³⁴³ The three types were anxiety elation psychosis (anxiety, ideas of reference, hallucinations, elation, and ecstasy), confusion psychosis (thought disorder, excitement or underactivity and poverty of speech), and motility psychosis (severe changes in psychomotor activity). A number of experts believe that the cycloid psychoses were a variant of bipolar disorder with an unusually sudden onset. Lithium has been shown to reduce the relapse in this group of disorders.

Mood disorders are divided into the depressive disorders (unipolar depression, UP), the bipolar disorders (BP), and two disorders based on aetiology (due to a general medical disorder or a substance). UP (major depression and dysthymia) are different from BP because there is no history of a manic, mixed or hypomanic episode. BP disorders (BP I, BP II and cyclothymia) involve the presence (or history of) of (a) manic, mixed or hypomanic episode(s), usually accompanied by the presence (or history of) of (a) major depressive episode(s).

[1] Major* depressive disorder: at least one major depressive episode (MDE; at least 2 weeks** of depressed mood or loss of interest accompanied by at least 4 additional symptoms from the following: - depressed mood most of the day on nearly every day, greatly diminished interest in most things or reduced capacity for pleasure, significant weight loss/gain or anorexia/hyperphagia, insomnia/hypersomnia, agitation/retardation, fatigue/loss of energy, worthlessness/guilt, reduced ability to think/concentrate/make decisions, recurrent thoughts of death/suicide with/without an attempt/plan).

[2] Dysthymic disorder: at least 2 years of depressed mood for more days than not plus additional symptoms that fail to meet criteria for MDE.***

[3] BP I disorder: at least one manic or mixed episode, usually with MDEs.

[4] BP II disorder: one or more MDEs with at least one hypomanic episode.

[5] Cyclothymic disorder: at least 2 years of numerous episodes of hypomania and depression not meeting criteria for mania or MDE.****

[6] Mood disorder due to a general medical condition or substance-induced.

[7] Mixed episode: at least one week in which criteria are met for both a manic and a MDE every day – rapidly alternating moods (sadness, irritability or euphoria).

[8] Mood disorder not otherwise specified (NOS, e.g. acute agitation).

One can then specify other details, e.g. severity/psychotic/in remission, chronic/with catatonic/melancholic/atypical features, or (if within 4 weeks of delivery) with postpartum onset.

Melancholic features: either of the following during the most severe period of the current episode – loss of pleasure in all/almost all activities or lack of reactivity to usually pleasurable stimuli (does not feel much better, even transiently, when something positive happens), and at least 3 of the following – distinct quality of depressed mood (not as felt after loss of a loved one), depression regularly worse in the mornings, early morning waking (EMW) by at least 2 hours earlier than normal pattern, marked psychomotor retardation/agitation, significant anorexia/weight loss, and excessive/inappropriate guilt.

Atypical features: mood reactivity (cheered by good news) plus 2 or more of – significant weight gain or increase in appetite, hypersomnia, leaden paralysis (heavy, leaden feelings in arms/legs), or a long-standing pattern of rejection sensitivity (not only when ill) that causes significant social/occupational impairment.

Seasonal pattern: regular temporal relationship between onset of MDEs in BP I or II or major depressive disorder, recurrent, and a particular time of year; full remissions (or change from depression to mania/hypomania) at a characteristic time of year; in the last 2 years, 2 MDEs that fulfil preceding criteria plus no non-seasonal MDEs have occurred during that same period; and seasonal MDEs substantially outnumber nonseasonal ones over the lifetime of the patient.

Rapid-cycling: at least 4 episodes of a mood disturbance in the past 12 months meeting criteria for major depressive, manic, mixed, or hypomanic episode.

*Implies significant disruption of mental function. Dropping somatic symptoms from the DSM-IV definition of major depression does not seem to make much difference to the end result (Zimmerman et al., 2010) and might be easier to apply to medically ill patients.

**Moore (2001) points out that this duration specifier does not take certain exceptions into account, e.g. very brief depression of the premenstrual syndrome and the extremely transient depression of partial seizures.

***As pointed out by Ghaemi (2003) dysthymia was included in DSM-III to capture those patients formerly diagnosed with neurotic depression. Ghaemi (2003, p. 18) stresses that most dysthymics also have episodes of major depression ('double depression') and often also have generalised anxiety disorder (GAD): 'mild chronic depression and anxiety often go together'.

****Mood changes may be sudden and difficult to predict. After the first 2 years, or 1 year in children and adolescents, one may diagnose superimposed BPI or II if appropriate. Borderline personality disorder (comorbid in at least 10% of cases) and ADHD (stimulants may worsen cyclothymia) must be included in the differential diagnosis.

DSM-IV-TR seasonal pattern specifier

'With seasonal pattern' can be applied to pattern of major depressive episodes in bipolar I or II or recurrent major depressive disorders if there is:

- regular temporal relationship between onset of major depressive episodes and a particular time of year unless there is some obvious reason (e.g. seasonal loss of job)
- full remission/shift in pole between depression/(hypo-)mania at particular time of year
- In last 2 years: 2 major depressive episodes defining above seasonal relationship with no non-seasonal major depressive episodes during that time
- Over a lifetime: seasonal major depressive episodes substantially outnumber non-seasonal major depressive episodes

Some clinical features in depression

Some depressives are agitated, others are retarded, whilst still others show a mixture of the two. In cases of relatively mild severity, resentment of others may be more prominent than guilt. Episodes vary in severity and in degree. They can be as short as days in duration, or they can last for so long as to be difficult to distinguish from personality disorder.¹³⁴⁴ About 10-20% of bipolars may experience a number of depressive episodes before having a manic one, and the risk for bipolar disorder may be higher in adolescent major depression and even higher in depressed children.(Dubovsky ea, 2003) On the other hand, in a 20-year follow-up study of 'unipolar mania' (Solomon ea, 2003) 20 out of 27 patients suffered depressive episodes. In a 15-year prospective study of consenting offspring of bipolar parents Duffy ea (2009) found that major mood episodes began in adolescence and not before this and nearly all index episodes were depressive, as were the first few recurrences.¹³⁴⁵ There were no cases of pre-pubertal mania. Severe, chronic bipolars may have neuropsychological dysfunction even when in remission. Also, sub-syndromal residual symptoms are common in bipolar disorder (Paykel ea, 2006) and are predictive of relapse.(Tohen ea, 2006)

Panic attacks, obsessions and compulsions, and delusions may be confined to depressive episodes and need not portend another disorder. Auditory hallucinations can be imperative, e.g. 'kill yourself!' Unpleasant tastes or smells can be experienced.¹³⁴⁶ A few severely depressed patients experience visual hallucinations. These may take the form of death or other scenes of destruction.

Depression can be associated with impotence in males or amenorrhoea in females.

Children and adolescents may have adult features of depression together with pain (head, abdomen, chest), separation anxiety or school refusal, unexplained fall in scholastic performance, over-eating and increased weight, and new conduct symptoms such as defiance and aggression.

Bipolar (BP) children may present with irritability, rapid cycling, mixed episodes, deteriorating function, and comorbid disorders (e.g. ADHD¹³⁴⁷), whereas adolescents may be psychotic, comorbid (drug abuse, conduct disorder), suicidal, and perhaps (in female manics) pregnant.(Murtagh & McNicholas, 2006) Wozniak ea (2010) found that the morbid risk for BP-I disorder in relatives of children with DSM-IV BP I was increased 4-fold compared to controls and 3.5 times over the risk to relatives of ADHD probands; the relatives of children with BP I also had high rates of psychosis, major depression, multiple anxiety disorders, substance use disorders, ADHD, and antisocial disorder when compared with controls; and familial rates of ADHD were similar for ADHD and BP I probands.

Dementia v Pseudodementia

Wernicke, in the 1880s, replaced the older term vesanic dementia with pseudodementia.¹³⁴⁸ He saw it as a chronic hysterical state. The concept has now broadened. Some of his cases may have had delirium. One common denominator in pseudodementia induction is the ability to impair cognition or to disable the mechanisms by which cognition is expressed. Depression and dementia may co-exist; both occur most

¹³⁴⁴ According to Morey ea (2010) a diagnosis of personality disorder made while the patient is depressed is valid and not an artefact of low mood because in their 6-year outcome study they found that the outcome for major depression 'with comorbid personality disorder' was similar to that of 'pure personality disorder' and much worse than for those with 'pure major depressive disorder'.

¹³⁴⁵ Of the 207 participants, 67 met DSM-IV lifetime criteria for at least one major mood episode.

¹³⁴⁶ One of the author's patients, whose depression only responded to ECT, described experiencing 'unbearable smells' early during a relapse, by which she meant that the smell of the kitchen upset her since she felt guilty at not feeling up to cooking for her family.

¹³⁴⁷ Is this true co-occurrence or criteria overlap? According to Luckenbaugh ea (2009) a period of elevated mood and reduced sleep in children favour a diagnosis of juvenile-onset BP over ADHD. According to Birmaher ea (2010) the preschool offspring of BP parents are at increased risk for ADHD and 'subthreshold' manic and depressive symptoms.

¹³⁴⁸ Arie (1983) defined pseudodementia as '...those disorders which present with the features of dementia but which on closer scrutiny or because of their subsequent course turn out to be of different origin...' and in old age 'the underlying disorder is most often depression'. 'Functional dementia' covers all non-organic dementia.

commonly around the same time in life. Pure depressive pseudodementia is associated with tardy responses, reduced speech output, and poor concentration without dysphasia or agnosia. (Carson et al., 2007, p. 330) The table outlines the main differences between both pure states. Since some cases of depressive pseudodementia will have cerebral atrophy, confusion may arise if CT data are taken in isolation.

Distinguishing pure depressive 'pseudodementia' ('dementia of depression', 'depression without sadness', 'cognitive impairment due to depression') from dementia (early cases)

Dementia

Early stages unclear, family are vague about duration
 Long presenting history
 Absent history of depression
 Slowly progressive symptoms
 No complaints of cognitive dysfunction and any complaints are vaguely expressed
 Patient conceals difficulties, exaggerates minor achievements, and struggles to achieve
 Patient uses calendars or note pads to aid memory
 Patient appears apathetic
 Mood is labile and shallow
 Social skills are often retained
 Behavior is in keeping with cognition
 Symptoms are worse at night
 Faulty attention and concentration
 Patient gives answers that are nearly correct
 Disorientation
 Poor memory for recent events
 Non-specific memory loss
 Fairly constant disability
 Abnormal EEG

Pseudodementia (depressive)

Abnormality obvious early
 Family can date onset and help is sought early
 Condition worsens quickly
 Positive past history
 Complaints of poor cognition
 Patient gives details of problems and emphasises difficulties
 Patient recognises failures more readily than successes
 Patient gives up and stops trying to keep abreast of things
 Patient complains a lot
 Pervasive mood change
 Early, severe loss of social skills
 Incongruent behavior and cognition
 Not worst at night
 Attention and concentration often good
 Unable to answer simple questions
 Appears to forget everything, remote and recent¹³⁴⁹
 Specific gaps in memory
 Variable performance

¹³⁴⁹ Cued recall may be better in depression than in dementia. (Dierckx et al., 2007)

Evidence for cognitive dysfunction before and after the onset of affective disorder

Impaired attentional or executive control of action (Clark ea, 2002; Cavanagh ea, 2002) - each episode may potentially make matters worse

Review of literature on cognitive impairment in bipolar (BP) patients - despite methodological shortcomings, cognitive dysfunction is a core and enduring deficit of illness (Ferrier & Thompson, 2002)
High correlation between depressive symptoms and cognitive impairment ($P < 0.001$) in 500 very old Dutch people - follow up showed accelerated annual increase of depressive symptoms associated with impaired attention, immediate recall, and delayed recall at baseline; but baseline depressive symptoms did not relate to an accelerated cognitive decline during follow up (Vinkers ea, 2004)

Neurocognitive impairment in euthymic BP that was not related to residual mood symptoms or hypercortisolaemia (Thompson ea, 2005)

Premorbid impairment of visuospatial reasoning in BP (and in other psychoses) (Tiihonen ea, 2005)

Healthy twins discordant for unipolar (UP) affective disorder had relatively poor cognitive performance on a wide range of functions, whereas healthy twins discordant for BP performed poorly on tests of episodic and working memory (Christensen ea, 2006)

While depressive symptoms in late life were cross-sectionally associated with impaired cognition they did not lead to cognitive decline (Ganguli ea, 2006)

Unaffected first-degree relatives of BP I patients had impaired psychomotor speed and slight impairment of executive function, but impairment verbal memory relates to the fully developed disorder.(Antila ea, 2007)

UP and BP in remission associated with neuropsychological impairment and such impairment differs between UP and BP cases and impairments are not attributable to affective symptoms or medication.(Stoddart ea, 2007)

Reduced verbal fluency in euthymic BP v healthy controls suggests disrupted prefrontal connectivity, especially in BP cases with many admissions, more episodes, and lifetime history of psychotic symptoms.(de Almeida Rocca ea, 2008)

Meta-analysis found deficient executive function and verbal memory in BP patients and, to a lesser degree, cognitive impairment in first-degree relatives; is this an endophenotype of BP?(Arts ea, 2008)

DSM-IV outpatients with major depression showed poor delayed recall related to current symptoms at presentation with depression but at second visit performance related more to past depression, suggesting a toxic effect (possibly on hippocampus) of depressive illness.(Gorwood ea, 2008)

Prospective UK and Chinese study of non-demented people aged at least 65 years suggests that only depression is predictive of dementia only if the depression is very severe.(Chen ea, 2008)

BP I patients perform worse than controls on measures of memory, attention, executive functions, and decision-making; the more past suicide attempts the worse the decision-making performance of patients and the greater the number of errors in *Stroop Colour Word Test*; small sample study wherein medication status was not controlled for.(Malloy-Diniz ea, 2008)

In DSM-IV major depression (HDRS > 17, aged 20-60 years, N = 48) more perseverative errors (PEs) on shortened WCST at admission predicted poorer clinical outcome at 3 months post-remission and discharge; poor event-based prospective memory and more PEs on the shortened WCST at admission predicted worse social and occupational outcome at follow-up.(Withall ea, 2009)

Cognitive testing on admission and prior to discharge (N = 53) and 6 months post-discharge (N = 20) suggests that cognitive impairment in UP depression are neither selective nor specific and that they resemble traits.(Reppermund ea, 2009)

Late-onset major depression is associated with greater impairment in verbal learning and memory and motor speed but not in executive function than is early-onset major depression, and the two groups did not differ in severity of depression, global cognitive function, intelligence or education; these findings were not due to ageing alone.(Thomas ea, 2009)

Impaired declarative memory is found in young women (age range 16-21 years) with no personal history of depression but with a depressed parent and this may be partly related to increased cortisol secretion.(Mannie ea, 2009)

Longer hospital admission in BP patients is associated with more severe deficits in executive functioning at discharge.(Levy ea, 2009)

Barrett ea (2009) found that first-episode bipolar disorder and schizophrenia subjects, relative to healthy controls, were most impaired in terms of memory, executive function and language but bipolar patients performed much better on tests of response inhibition, verbal fluency and callosal function; and the differences could be explained by the greater likelihood of schizophrenia cases to be globally impaired and to have negative symptoms.

Doyle ea (2009) found cognitive impairments in BP youth (mean age 12.3 years) and problems with abstract problem-solving and working memory in their well siblings (endophenotype?).

Patients with BP or schizophrenia showed deficits in extra-dimensional set shifting (must learn new stimulus-reward associations based on different types of stimuli) and reversal learning (shift of attention to a novel but previously irrelevant stimulus),(McKirby ea, 2009) probably due to disrupted networks involving ventral prefrontal cortex.

Cognitive impairment and time spent in subsyndromal depression may be associated with worse long-term functional outcome in BP.(Martino ea, 2009)

Drug-free and medicated euthymic BP patients do not differ in their neurocognitive deficits, suggesting that the latter are an integral part of BP.(Goswami ea, 2009)

In a first-episode psychosis study Zanelli ea (2010) patients with schizophrenia had widespread neuropsychological impairments; subjects with other psychoses and depressive psychosis also had widespread problems; and those with BP or mania had less pervasive difficulties but had problems with verbal memory and fluency tests

Results of a large-scale extended Latino pedigree study of cognitive functioning in BP (Glahn ea, 2010) suggested that measures of processing speed, working memory, and declarative (for faces) memory may be candidate endophenotypes for that disorder.

Half of patients aged at least 60 years with DSM-IV major depression had generalised cognitive impairment that persisted after 18 months; at 4 years follow-up impairments persisted but did not decline further, suggesting a trait rather than state relationship.(Köhler ea, 2010)

P2 and late positive event-related brain components examined during a free recall task in 3 groups: current depression, remitted depression, and healthy people: normals and remitted cases (but not the currently depressed) had increased recall of positive self-referent items (SRIs); greater component amplitudes in response to negative relative to positive SRIs were found in current and remitted depressives during automatic processing stage as indexed by P2 component and (indexed by late positive component) in the currently depressed during effortful encoding.(Shestyuk & Deldin, 2010)

Depression in women

Depression in women has been studied by a number of workers. Depressed females are more likely to report a poor early relationship with their mothers, but not with their fathers, low care and high overprotection, a poor marriage, poor current relationships with their own mothers, much poorer relationships with parents-in-law, and more poor family relationships in general.

Fatigue and anxiety symptoms, both psychic and somatic, are said to be very common in depressed women. However, some authors find no difference in symptomatology between depressed men and women.

The puerperal psychoses (usually come on after day five) are psychotic depression (most cases - one in 500 live births), schizophrenia-like (a minority), and toxic confusional ('childbed fever' – rare today).(O'Shea, 2000a; Jones & Smith, 2009) The clinical picture may change suddenly. The patient may appear confused, perplexed, and bewildered. Mood may be low or elevated or extremely labile. The content of delusions and hallucinations may refer to the baby. BP disorder carries a high risk of puerperal psychosis.

It is usually stated that the evidence is against a direct aetiological connection between depression and the menopause¹³⁵⁰,(O'Shea, 2000b) although this important event can mean freedom for one woman and perceived loss of role for her sister (the same applies to conditions such as endometriosis). Freeman ea

¹³⁵⁰ **Menopause:** As the function of ovaries decline, pituitary LH and FSH increase. The latter are best measured shortly after menstruation (their lowest concentration is expected at this time) since levels may rise to premenopausal figures later (with highest recordings midway through the cycle).

(2004) found increased likelihood of depressive symptoms during transition to the menopause and a reduced likelihood after the menopause; increasing oestradiol (estradiol) levels were associated with depression whereas greater age and a rapidly increasing FSH profile appeared to be protective. New onset and recurrence of major depression may be more likely at the perimenopause in women with a history of premenstrual syndrome or postpartum depression. (Parry, 2008) Bromberger ea (2009) found that a lifetime history of anxiety disorder and role limitations caused by poor physical health at baseline and a particularly stressful life event were predictive of first episode major depression in middle-aged women whereas vasomotor symptoms were not. Using the Center for Epidemiological Studies Depression Scale (CES-D) in a longitudinal US community study, Bromberger ea (2010) found that the perimenopause and postmenopause were associated with higher CES-D scores than was the premenopause and the following factors were associated with increased scores: larger increase in testosterone from baseline, less education, being Hispanic, vasomotor symptoms, stressful life events, and low social support.

Mood disorders in youth

Depression is more likely in adolescence¹³⁵¹, especially in females, but is still not uncommon even in early childhood, when it is possibly commoner in boys. Depression before puberty may present as physical concerns, agitation/anxiety/phobia, or avoidance of other people. The depressed adolescent may show poor academic performance, feelings of not being listened to or of not being understood, antisocial or aggressive behaviour, negativism, restlessness, alcohol/substance abuse, or avoidance of other people. Subjective complaints of depression should be sought in childhood because the disorder may be missed if too much reliance is placed on parental information. Childhood depression is often comorbid with other psychiatric conditions such as phobic or conduct disorders. Social disadvantage, parental problems, cognitive difficulties, chronic medical problems (e.g. epilepsy, diabetes, or asthma), and other factors may be positively correlated with early depression. The children of depressed parents with so-called major depression have an increased risk of depression, which may come on early in life, and a variety of behavioural problems, such as drug abuse and accident-proneness. Treating their parents' depression may help to decrease the morbidity levels of the offspring. Having a biological parent who suffers from a severe or chronic depression is associated with future adaptational problems in their offspring. Depression in the mother is generally considered to be more strongly associated with increased psychopathology in the children than is depression in the father. However, depression in the father during the postnatal period can have adverse and persistent effects on the emotional and behavioural status of their children. (Ramchandani ea, 2005; Lewinsohn ea, 2005) Also, Marmorstein ea (2004) found that depressed mothers tend to partner with antisocial fathers, which may at least partly account for depression and conduct disorder in offspring. However, Tully ea (2008), using an adoption paradigm¹³⁵², found that maternal, but not paternal, depression was associated with lifetime diagnoses of major depression and disruptive disorders in adolescents. In one study, compared with early onset unipolar depressives, early onset bipolar cases had experienced delayed language, social or motor development, delay being most marked in those who developed psychotic symptoms. (Sigurdsson ea, 1999) Weissman ea (2006) compared offspring of depressed parents with those of non-depressed parents over a period of 20 years and found a threefold increase in risk for anxiety disorders, major depression, and substance dependence in the former group; these people were also more likely to be socially impaired, and, as they entered middle age, to have increased medical morbidity and mortality. Timko ea (2008) followed up the offspring of depressed parents for 23 years and found that they had an excess of depression and disability in adulthood. Treatment of depression to remission in the mother leads to decreased psychiatric symptoms and better functioning in offspring. (Pilowsky ea, 2008)

Hazel ea (2008) found that continued stress close in time to onset of depression was the most important factor in the association between early adversity and depression in late adolescence. TV exposure and total media exposure in adolescence were found to be associated with increased odds of depressive symptoms in young American adults, particularly in males. (Primack ea, 2009)

¹³⁵¹ The 6-item Kutcher Adolescent Depression Scale (KADS: LeBlanc ea, 2002) is a self-report instrument that asks about mood, self evaluation, energy/motivation, derivation of satisfaction from life, anxiety/worry, and suicidality 'over the last week'. A score of 6 or more indicates a need for more thorough assessment.

¹³⁵² To test for environmental effects as distinct from genetic influences.

The current view regarding treatment of mildly depressed children and adolescents is to try non-drug approaches (e.g. CBT if available) at first but that medication be added if initial therapy fails. For moderate to severe cases combined psychotherapy-medication is advocated with family/parental therapy/education¹³⁵³ as needed.(Schloredt ea, 2008, p. 808; Thapar ea, 2010) Most studies involving SSRIs have tended to include milder, uncomplicated cases (see Bridge ea, 2009), making clinical extrapolation difficult. Medication-placebo differences may be underestimated for severe depression in these trials. Nevertheless, medication studies suggest that 4 out of 10 cases do not respond to medication and that relapse following acute response is very common. Also, the natural history of depression is to remit eventually, with 7 out of 10 cases doing so by 72 weeks.(Goodyer ea, 2003) Emslie (2008) points out that less than half of American children and adolescents receive any treatment for depression and that follow up of cases prescribed medication is infrequent¹³⁵⁴ with the inevitable consequences of low adherence and effectiveness rates. Another reason why medication may not be very effective in childhood may be the high comorbidity levels, the latter not being responsive to antidepressant drugs. TCA trials have tended to be small in numbers and short in duration. There is slightly more evidence for efficacy for the SSRIs than for TCAs in childhood depression. The Committee on Safety of Medicines in the UK has stated that, of the SSRIs, only fluoxetine should be used in young people. In one US study of adolescents with major depression 61% improved with fluoxetine alone whereas only 43% improved with CBT alone, the latter not being significantly better than those on placebo (35%).(Domino ea, 2008) Fluoxetine was more cost-effective than combination treatment at 12 weeks. The FDA in the US labels only fluoxetine for use in children with major depression. Ramchandani (2004) has called for more openness in the making of such dramatic decisions; Wagner ea (2004) found citalopram to be safe and efficacious in depressed children and adolescents; Rynn ea (2007) found short-term efficacy for sustained-release venlafaxine in children and adolescents with generalised anxiety disorder; Whittington ea (2004) has pointed out that the non-publication of trials may lead to erroneous recommendations for SSRIs in childhood; and Pfeffer (2007) tells us that the FDA was not against using SSRIs in children but rather was trying to improve monitoring! The FDA paediatric warning led to a fall in new adult diagnoses of depression and a fall in antidepressant prescribing without a compensatory increase in other treatments such as psychotherapy¹³⁵⁵, (Valuck ea, 2007) and a rise in suicide rates in children and adolescents!(Gibbons ea, 2007a) However, others (Wheeler ea, 2008) found no attributable change in suicidal behaviour in young people in England following regulatory action in 2003 to restrict SSRI use in under 18s. It is difficult to know if these discrepancies relate to clinical reality (including high non-compliance rates) or to problems inherent to statistical analysis (e.g. the definition of clinical significance).(Turner & Rosenthal, 2008)

Review and meta-analysis of 27 paediatric antidepressant RCTs (Bridge ea, 2007)

Overall, small (< 1%) increase in emergent suicidal ideation/attempt (no completed suicides)

Efficacy: strongest for non-OCD anxiety, intermediate for OCD, more modest for major depression

Advise cautious, monitored use of antidepressants as one first-line option

Collaborative discussion with family and patient

Systematic review/meta-analysis of 30 trials of antidepressants in juveniles (Tsapakis ea, 2008)

All antidepressants have more or less modest effects

Fluoxetine possibly more effective, especially in adolescence

Need studies of severe/hospitalised/suicidal depression and childhood depression

More research is needed into interpersonal therapy in this age group. Cognitive therapy may not be as effective in severe as in 'mild to moderate' depression.(March ea, 2004) Also, Goodyer ea (2007) found no additional benefit of adding CBT to SSRIs and routine care in adolescents with 'moderate to severe' depression. Fristad ea (2009), in study involving children aged 8-12 years old with depression or bipolar disorder, compared the effects of adjunctive multifamily psychoeducational psychotherapy (8 x 90 minute

¹³⁵³ However, whilst it is often stated that family discord is aetiologically influential in depressed youth, family therapy, at least in research, may add little.(Schloredt ea, 2008, p. 812)

¹³⁵⁴ Despite FDA advisory of 2003 to provide frequent follow up.(Morrato ea, 2008)

¹³⁵⁵ Libby ea (2009) found that psychotherapy increased for adult but not paediatric cases.

sessions) with treatment as usual and found improved outcomes for the multifamily intervention at follow up.

Longer duration of treatment of adolescents with depression with CBT and/or fluoxetine appears to be more effective than shorter treatment. (Treatment for Adolescents with Depression Study [TADS] Team, 2009)

ECT, whilst rarely used in young people¹³⁵⁶, has been shown to be acceptable to such patients. (Walter et al, 1999)

Childhood bipolar disorder (BP) is diagnosed more often in the US than in Europe. It is associated with irritable mood, cyclical changes in mood, and an increased risk of comorbid ADHD. Mood episodes may be less discrete than those found in adults and BP may instead take a prolonged and undulant course in children. Birmaher et al (2009) reported that bipolar spectrum disorders (BP I and II and NOS) in people aged 7-17 years were episodic, sub-syndromal more often than syndromal, with mainly depression, mixed symptoms, and rapid changes in mood. Tijssen et al (2010) in Munich followed up adolescents and young adults for 10 years and found that persistent affective symptoms in earlier life predicted later development of BP in a dose-response fashion; although hypomanic symptoms were relatively common in adolescence most such cases resolve with the passage of time. The findings of a Dresden (Germany) study by Beesdo et al (2009) of 3,021 community subjects aged 14-24 years at baseline and 21-34 years at third follow-up are shown in the box.

Incidence and conversion of mood episodes/disorders in first 3 decades of life (Beesdo et al, 2009)

Estimated cumulative incidence at age 33 years = 2.9% for manic, 4% for hypomanic, 29.4% for major depressive, and 19% for minor depressive episode

Overall, 26% had unipolar major depression, 4% bipolar depression, 1.5% unipolar mania, and 3.6% unipolar hypomania

Overall, 0.6% and 1.8% had unipolar mania or hypomania respectively

3.6% of initial unipolar major depressives developed (hypo) mania, with especially high rates in adolescent onset depression (< 17 years: 9%)

49.6% of initial unipolar mania cases subsequently developed major depression and 75.6% major or minor depression

These results suggest that unipolar and bipolar cases are more common in adolescents and young adults than was previously believed. However, in an 8-year NIMH-sponsored study, only 62.6% of bipolar I disorder children were found by Geller et al (2010) to have received anti-manic medication at any time, especially so if they were recruited from paediatric (versus psychiatric) sites ($p = 0.006$). They were more likely to get treatment for ADHD or depression. Earlier recovery was predicted by greater length of time on lithium ($p = 0.17$).

Mood disorders in the elderly

Although reported figures vary greatly, about 15% or more of people over age 65 years have significant symptoms of depression, one-fifth or less of these having severe depression. The American ECA study found an overall prevalence of major depression in people over 65 years of age of one in one hundred (1.4% in females, 0.4% in males), and about 20% had subsyndromal depressive symptoms¹³⁵⁷. (Koenig & Blazer, 1992) McDougall et al (2007) found a depression prevalence of 8.7% in over-65s in England and Wales (10.4% women, 6.5% men). For ill understood reasons¹³⁵⁸, the figures for major depression are

¹³⁵⁶ ECT is reserved for treatment-refractory and/or very urgent cases in this age group.

¹³⁵⁷ Subsyndromal depression is not uncommon in the elderly in East Asia, with a prevalence of 8-9%. According to Heok and Ho (2008) risk factors include poor health, brain injury, low B12 and folate, and raised plasma homocysteine levels. Chronic pain in the elderly increases the likelihood of suicidal thinking. Depression is a risk factor for cardiovascular disease and for mortality in coronary heart disease.

¹³⁵⁸ Cohort effect, somatisation (hypochondriacal presentation versus difficulties in differentiating from physical illness), underreporting (e.g. patient unwilling to admit to depression or more experienced at handling difficulties; others viewing low mood as normal in old age), cognitive impairment (dementia of depression), dementia, coexisting disorders, etc.

arguably¹³⁵⁹ lower than in younger people. While some authors claim that depression becomes more common with increasing age, it appears that mania does not. The seriousness of subthreshold cases should not be underestimated.(Beekman ea, 2002) Indeed, when such subthreshold/minor¹³⁶⁰ cases are included rates of depression increase with age,(Snowden, 2001) at least in women.(Wu & Anthony, 2000) The boring atmosphere of the average nursing home is a hotbed of demoralisation. A depressive episode is more likely to follow a manic episode in old age.(Broadhead & Jacoby, 1990) Long-standing inability to form close, confiding relationships may confer vulnerability to depression in the elderly. Müller-Spahn and Hock (1994) listed the most frequent problems in this vulnerable group as social isolation, loss of important support systems, loss of autonomy due to psychiatric and physical illness and physical disability, inactivity consequent upon retirement, loss of reputation and finances, residence relocation, and severe insomnia. (Indeed, sleep disturbance is an independent risk factor for recurrence of depression in the elderly: Cho ea, 2008) It has been suggested that the perception of support may be more germane than the actual level of support. Older people are likely to be taking many different medications, and some of these (e.g. corticosteroids) may act directly or indirectly as depressogens.(Alexopoulos ea, 2001) Confusion/delirium should be considered before mislabelling someone as having drug-induced depression.(Cassem ea, 2004, p. 72)

Cerebral atrophy (Baldwin ea, 2005) and reduced right frontal lobe volume (Almeida ea, 2003) have been described in late-onset depression.

Penninx ea (2001) suggest that depression increases the risk cardiac mortality irrespective of any baseline heart disease and Surtees ea (2008) found that major depression was associated with a persistently increased risk of ischaemic heart disease (IHD) mortality independent of established risk factors for IHD¹³⁶¹. Linke ea (2009), in a study of women with suspected myocardial ischaemia, found that somatic but not cognitive/affective depressive symptoms (using the BDI) were associated with increased risk of cardiovascular mortality and events¹³⁶². These findings were confirmed by Martens ea.(2010) Lavretsky ea (2010) followed up a sample of elders from the community and from memory clinics and 35% died during the study; cognitive impairment, age, male sex, depressed mood, and having lacunes on MRI predicted higher mortality, and having both lacunes and depression was associated with the highest mortality risk. Depressed patients with heart disease are less likely to adhere to diet, exercise, and prescribed medication.(Whooley ea, 2008) Cardiovascular mortality is higher in elderly men whose depression is inadequately treated¹³⁶³ than in those where adequate therapy is administered. Cardiovascular mortality is higher in elderly women who are not given ECT than in those who receive it.(Babigian & Guttmacher, 1984) Of course, the same vascular pathology may play a role in the aetiology of elder depression, (Kim ea, 2004) genes playing a lesser role than in younger cases of depression¹³⁶⁴. It has been suggested that SSRIs may reduce mortality in depressed patients from cardiac disorders by their effects on platelets.(Serebruany ea, 2005) It should be noted, however, that trials of SSRIs and mirtazepine conducted in cardiac patients are few in number.(Anonymous, 2008)

Elderly with risk factors for vascular depression have (vs old depressed people without such risk factors: Alexopoulos ea, 1997)

Increased cognitive impairment and disability

More impaired fluency and naming

More retardation

Less agitation

Less insight

(Represent damage to the striato-pallido-thalamo-cortical pathways and other brain areas?)

¹³⁵⁹ An 8-year Rotterdam follow-up cohort study of community-dwelling elderly (Luijendijk ea, 2008) found the incidence rate of depression to be low except when 'clinically significant' depressive symptoms were accounted for. Most late-life depression occurred in people with a history of depression. Also, recurrence rates were the same for both sexes.

¹³⁶⁰ Dysthymia and minor depression are included in this group.

¹³⁶¹ E.g. an episode of major depression during the previous 12 months meant that a person was 2.7 times more likely to die over the 8.5-year follow-up.

¹³⁶² CVA, MI, and CCF.

¹³⁶³ Ryan ea (2008) suggest that treatment resistance in elderly men reduces their chances of survival.

¹³⁶⁴ Homocysteine might promote cerebrovascular disease and reduce neurotransmitter levels thereby causing low mood.(Folstein ea, 2007)

Cardiovascular disease is overrepresented in patients with a history of mania or hypomania compared to subjects with a history of only a major depressive episode or no mood episode. (Ramsey ea, 2010) Depression in adolescents, older men, and women has been reported to correlate with lower birth weight, (Thompson ea, 2001a; Patton ea, 2004; Gale & Martyn, 2004) perhaps indicating a neurodevelopmental aetiology.

Sackeim ea (2000) emphasise that encephalomalacia¹³⁶⁵ may relate to vascular insufficiency in subcortical water-shed areas¹³⁶⁶. There is a compensatory mismatch between metabolism and cerebral blood flow (CBF), i.e. CBF is diminished but oxygen uptake by tissues increases. CO₂ is a strong cerebral vasodilator. Acetazolamide increased CO₂ levels. However, in the elderly depressed there is a reduced white matter response to acetazolamide, i.e. the hypercapnic challenge with acetazolamide demonstrates a reduced ability to vasodilate.

Tiemeier ea, (2004) in a cross-sectional population-based Rotterdam study, found that atherosclerosis and depression are associated in the elderly. The more severe was extra-coronary atherosclerosis the higher was the prevalence of depression. There was a strong relationship of severe coronary and aortic calcifications with depressive disorders.

White matter changes predate and are associated with late-life depressive symptoms. (Teodorczuk ea, 2007) Lower folate, lower B12, and raised homocysteine may be risk factors for late-life depression. (Kim ea, 2008; Almeida ea, 2008) Comprehensive neuropsychological function and white matter hyperintensity severity on MRI predicted MADRS scores over 12 weeks of sertraline treatment of major depression in subjects aged over 60 years; baseline neuropsychological function differentiated those who would remit from those who would not remit and predicted time to remission. (Sheline ea, 2010)

Depression in the elderly is often missed because it is commonly mimicked by somatic illness and *vice versa* (e.g. weight loss); the elderly often minimise feelings of sadness and are physically preoccupied; and neurotic complaints, such as obsessions, anxiety, and hypochondriasis, may obscure depression.

Neuroticism is itself associated with recurrence of depression in later life. (Steunenberga ea, 2009) Lenze ea (2001) suggest that 85% of elderly depressives have significant comorbid anxiety. The consequences of missing the diagnosis (Müller-Spahn and Hock, 1994) are loss of quality of life, social isolation, increased mortality (suicide), increased vulnerability to certain diseases, admission to a nursing home, and a large financial burden. Depression is common in nursing homes, factors contributing to this being loss of independence and familiar surroundings, reduced contact with family and enjoyed activities, and physical disorders. (Feliciano & Areán, 2007, p. 294)

Chief risk factors for depression in physically ill elderly people (Katona & Livingston, 1997, p. 11)

- Female (but under 85 years of age)
- Positive personal psychiatric history
- Severe physical illness
- Significant functional disability

Note: adjustment disorder with depressed mood is not uncommon in the physically disabled or chronically ill elderly (Blazer, 2003, p. 1546)

Most important symptoms in diagnosing depression in older people (Alexopoulos ea, 2001)

- Sad and downcast mood
- Feeling blue
- Frequent crying
- Recurrent thoughts of death/suicide.

According to Baldwin ea (2002, p. 10) whilst depression in older people often resembles that in younger people, it may be modified by less emphasis on sadness and more on hypochondriacal and somatic

¹³⁶⁵ Synonymous with leuko-araiosis, subcortical arteriosclerotic encephalopathy, hyperintensities, unidentified bright objects or UBOs. Deep white matter lesions have been found on MRI in some young BP cases. (El-Badri ea, 2006) For **diffusion tensor imaging studies** see Alexopoulos ea (2008), and Bruno ea (2008) who found frontotemporal white matter abnormalities (of unknown pathology) in BP.

¹³⁶⁶ Areas with a poor collateral blood supply.

concerns, poor subjective memory function or 'pseudodementia', marked anxiety, and apathy as well as poor motivation. In an Irish community dwelling sample of people aged 65 years and older Gallagher *ea* (2009) found that, compared to early-onset depression, among those with depression commencing at age 60 years or more (late onset) there was less likely to be a positive family history of depression, less reporting of prior hospital admission for depression, greater cognitive impairment, less feelings of guilt, and less thoughts that life was not worth living. Nevertheless, the authors could find no distinct profile of depressive symptoms that helped to distinguish early versus late onset cases at an individual level.

Saez-Fonseca *ea* (2007) found that depressive pseudodementia in the elderly may be a harbinger of dementia with most cases having an established dementia 5 years later!

A Dutch study of depression in people aged 55 years or more (Licht-Strunk *ea*, 2009) found a median duration of major depressive episode of 18 months; 35% recovered within a year, 60% within two years, and 68% within three years; and poor outcome was associated baseline depression severity, a family history of depression, and poorer physical functioning (the latter only improved if the patient recovered from depression).

An American geropsychiatry expert consensus included the following (from first choice onward): the top-rated antidepressants were SSRIs¹³⁶⁷ (citalopram, sertraline, and paroxetine); if a TCA was to be used, nortriptyline was first choice (followed by desipramine); CBT, supportive, problem solving, and interpersonal, but not psychodynamic, psychotherapies were favoured and choice depended on needs and resources; persistence in treating the elderly depressed was stressed; and the duration of successful drug therapy related to number and severity of episodes, difficulty in bringing an episode under control, and persisting anxiety.

Elderly depressives spend significantly longer as in-patients than do their younger counterparts, they take longer to respond to treatment, and relapse is common. They often require indefinite antidepressant treatment. ECT may be more effective in the elderly depressive than in younger patients. (Tew *ea*, 1999) Maintenance ECT, e.g. once monthly, may be required in some subjects in order to maintain a response. Lithium does work in the elderly. However, they are susceptible to illnesses that can reduce glomerular filtration rate (GFR) and thereby precipitate toxicity, and they are often taking drugs that interfere with lithium clearance, especially thiazide diuretics and NSAIDs. According to Baldwin *ea* (2002, p. 67) TCAs may be superior to SSRIs in the treatment of the severely depressed elderly inpatient. Lofepamine is safer than the older TCAs. (Baldwin *ea*, 2002, p. 73) Before starting a TCA the patients blood pressure should be measured lying and standing: a drop of 20 mm Hg or more is likely to be made worse by TCAs, with the danger of falls. This is more likely if the patient is taking diuretic medication or has poor left ventricular function. Generally, before starting any antidepressant in the elderly one should steer clear of any drug that might exacerbate any underlying medical illness or interact with other prescribed medication¹³⁶⁸. The importance of psychosocial support cannot be underestimated, even when antidepressant drugs are used. (Roose *ea*, 2004) Guidance (based on algorithms) offered to primary care physicians by care managers and assistance given to older patients with adherence kept patients in treatment, reduced suicidal thinking, and improved outcomes of major depression at two years. (Alexopoulos *ea*, 2009) Steffens and Potter (2008) emphasise the need to help elderly depressives with cognitive problems by focusing on practical problem-solving strategies. (see Alexopoulos *ea*, 2003)

Comorbid axis I disorders, including panic disorder, are common in elderly bipolar disorder patients. (Goldstein *ea*, 2006) Scheurich *ea* (2008) suggest that motivational difficulties influence cognitive difficulties in older depressives and recommend employing goal-setting theory in its alleviation (basically such patients perform better if assigned specific, difficult goals than when asked to reach vague or easy ['do your best'] goals). Thompson *ea* (2001b) could not demonstrate a clinically important difference between CBT and antidepressant medication in reducing depression severity in mild-to-moderately depressed elderly outpatients. Lenze *ea* (2003) found little effect of co-morbid anxiety on outcome of late-life depression treated with interpersonal psychotherapy.

Depression in the workplace

¹³⁶⁷ Risk of hyponatraemia and small increase in risk of falls. (Lam & Mok, 2008, p. 81)

¹³⁶⁸ TCAs may increase the risk of hypotension and arrhythmias (is the patient on quinidine?) in a patient in the cardiology ward. Venlafaxine may worsen hypertension. Drugs that promote weight gain – TCAs or mirtazapine – may destabilise diabetes. Take care with SSRIs and codeine combination or fluvoxamine and warfarin given together.

Excessive workload and extreme time pressures increase the risk of major depression and generalised anxiety disorder compared with low occupational demands.(Melchior et al, 2007) Warning signs of depression in the work situation include absenteeism, reduced productivity, poor moral and lack of co-operation, uncharacteristic accidents, frequent complaints of aches and pains, poor decision-making, indecision, and alcohol or drug abuse.

Recurrent brief depression

This is a relatively new innovation that is said to be common and have a relapsing course. One in twelve people may be affected and the risk of deliberate self-harm may be 13% over ten years. Depressive symptoms last on average for three days. Diagnostic criteria include 3 episodes over 3 months, depressive episode lasting less than 2 weeks, and no association with the menstrual cycle. The usual treatments for depression may be given a trial, although it may be relatively unresponsive to antidepressants (Baldwin, 2003) because episodes may be too short. Problem-solving strategies may reduce any tendency to self-harm.(Baldwin & Hirschfeld, 2005, p. 63) Alcohol and benzodiazepines are best avoided. DSM-IV lists this disorder 'for further study'.

Chronic depression

Scott's (1988) classification of chronic depression

Chronic primary major depression: usually late onset; unresolved major depressive episode without evidence of a pre-existing chronic minor disorder; may have a unipolar or a bipolar disorder

Chronic secondary major depression: unremitting major depressive illness secondary to a physical illness or non-affective psychiatric disorder

Characterological or chronic minor depression: dysthymic disorder, a heterogeneous group of patients with ill-defined onset in early adulthood - it appears to be part of the character style; symptoms are with relatively minor - in 1980, the APA replaced 'neurotic depression' with 'dysthymic disorder'. Dysthymia has been attacked as an ill-defined, catch all, non-specific label.

'Double' depression: acute major depressive episodes superimposed on underlying dysthymia, the patient returning to the latter after recovery; prognosis for minor symptoms is poor and recurrence of major depressive episodes is frequent.

Factors that may predict chronicity are female sex, especially if the premorbid personality contains neurotic traits, childhood adversity¹³⁶⁹, current interpersonal problems, unipolar disorders, and a high family loading for unipolar disorders. Also of significance are the adequacy and appropriateness of treatment received, and the duration of the illness episode prior to starting therapy.

Other conditions

In 1882, the French psychiatrist Jules Cotard (1840-89), described patients with what he called *délire de négation*, the term *Cotard's syndrome* being first used by J Seglas in 1897. This consists of a severe depressive state with nihilistic delusions (e.g. "my bowels are rotten" or loss of money, health, strength, social status, etc). These can expand to negate the patient's whole internal and external world. The hallmark is the delusion of being dead. Associated features include *le délire d'énormité* or delusion of enormous body size or a delusion that urinating will flood the world, and delusion of immortality. Cotard's syndrome may require many applications of ECT to induce a remission. There is even a case report of remission after two grand mal seizures.(Malone & Malone, 1992) Cotard's syndrome has accompanied non-dominant frontotemporal lesions, the delusions subsiding with anticonvulsant therapy. CT studies suggest that Cotard patients may have brain atrophy and medial frontal lobe disease. Cotard's syndrome may be associated with valaciclovir (Halldén et al, 2007) or may complicate Parkinson's disease.(Factor & Molho, 2004) *Prasad's (1985) syndrome* is due to Hashimoto's thyroiditis but presenting as treatment-resistant mania in a patient of good premorbid personality. Antipsychotic drug-resistant cases have responded to thyroid hormone replacement. Onset may be acute.

Lycanthropy is the belief that one is transformed into an animal, classically a wolf or werewolf. This non-specific presentation can be associated with 'hysteria', bipolar affective disorder, psychotic depression, schizophrenia, or organic brain disorders.

¹³⁶⁹ Parental indifference, family violence, sexual abuse.

'Minor depression'

This category is listed in DSM-IV as an area 'for further study'. Essentially, the criteria are (a) one or more episodes of depressive symptoms that fulfil the duration criterion for major depression but there are fewer symptoms and less impairment, and (b) the following diagnoses are outruled: adjustment disorder with depressed mood¹³⁷⁰, depressive disorder not otherwise specified, major depressive episode, dysthymia, cyclothymic disorder, periods of normal sadness, uncomplicated bereavement, mood disorder induced by substance/general medical condition, a history of major depressive /mania/mixed episode(s), and depressive symptoms that occur exclusively during schizophrenia or schizophreniform/schizoaffective/delusional/not otherwise specified psychotic disorders. Baldwin ea,(2002, p. 108) extrapolating from mixed-aged populations, suggest that minor and major depressions may form part of a continuum rather than separate disorders.

Major depressive disorder (MDD) with anger attacks

About one-third of ambulant MDD cases have abrupt, easily provoked anger outbursts associated with autonomic hyperactivity. Anger, verbal or physical, is most commonly directed at loved ones. Such attacks may have a basis in low central 5-HT activity.(Fava and Rosenbaum, 1999)

Mania

The death rate in hospitalised manics before the mid-1930s could be as high as 20%, almost half succumbing to exhaustion.(Derby, 1933) Hypomanic patients rarely present for treatment of their own volition. The differential diagnosis of mania includes cyclothymia, schizophrenia, schizoaffective disorder, frontal lobe syndrome (including leucotomy), secondary mania, medications (steroids, L-DOPA, bromocriptine, INAH, etc.), stimulants (cocaine, amphetamine), and various CNS disorders such as basal tumour, encephalitis, and right hemispheric cerebrovascular disease. Mania may be precipitated by sleep deprivation in people who are euthymic, depressed, or who have no history of prior mania. 'Continual sleeplessness' was listed among the causes of mania by Soranus of Ephesus¹³⁷¹.(Brown, 2004, p. 440) In fact, a study involving university students with cyclothymia or bipolar II disorder and healthy controls suggests that both diagnosis and lack of regular activities predict time to first prospective onset of major depressive, hypomanic, and manic episodes.(Shen ea, 2008) A 'manic switch'¹³⁷² from medication has been reckoned to occur in 11.2% of patients on TCAs, 3.7% of people on SSRIs, and 4.2% of individuals receiving placebo. The risk of such a switch occurring in predominantly unipolar depressives has been put at <1%.(Post, 1994) Bupropion was associated with less manic episodes in bipolar patients followed up for one year than was desipramine in one study (11% v 50%: APA, 2002, p. 597) and, in another study, switches to hypomania or mania in bipolar depressed patients occurred in 3% of paroxetine-treated patients and 13% of venlafaxine-treated cases.(APA, 2002, p. 596¹³⁷³) The combination of an antidepressant and a mood stabiliser leads to less switching into mania in bipolar II than in bipolar I patients.(Altshuler ea, 2006) However, the combination may be no better than using a mood stabiliser on its own.(Sachs ea, 2007) The mechanism of switching is unknown¹³⁷⁴. We do know that chronic TCA treatment reduces sensitivity to DA autoreceptors; such downregulation might cause increased dopaminergic activity and mania. According to Vieta,(2004) quetiapine (for mania) may not be associated with treatment-emergent depression. Current or past substance use in depressed bipolar patients was not associated with longer time to recovery but may have increased risk for switching directly into mania/hypomania/mixed states in an American study.(Ostacher ea, 2010)

Symptoms of mania

'Infectious' jollity - the patient is funny

¹³⁷⁰ Marshall ea (2008, p. 591) speculate that up to one-fourth of cases diagnosed as 'anxiety' or 'depressive' disorders actually have adjustment disorders that will get better without much in the way of intervention.

¹³⁷¹ 98-138 AD.

¹³⁷² From a depressed to a manic state; confusingly sometimes called 'bipolar III disorder' – 'IV' if the switch follows ECT.

¹³⁷³ See also Post ea. (2006)

¹³⁷⁴ Rarely, mania, extrapyramidal symptoms, and akathisia may follow termination of antidepressants.(Haddad & Anderson, 2007)

Pressure of speech¹³⁷⁵
 Flight of ideas
 Psychomotor overactivity
 Distractibility
 Sexual disinhibition
 Reduced need for sleep
 Grandiosity
 Poor judgement
 Insightlessness¹³⁷⁶
 Psychotic symptoms (if present): e.g. grandiose or paranoid delusions
 Crying spells
 Everything seems clearer - colours are brighter and contours are very sharply defined; patient may say his thoughts are of exceptional clarity
 Instead of elated mood there may simply be unconcern and unusual friendliness
 Older persons may present with irritability or mixed states with depressive symptoms (ideas have depressive content but are expressed in a jocular way), so-called 'miserable mania'
 May report visions, which may have a religious content

Late life onset mania is less likely to be associated with a positive family history compared to early onset cases; it may be due to brain changes, or brain changes might modify early onset cases. First onset mania in later life may be associated with increased vascular risk factors¹³⁷⁷ and relatively high current serum cholesterol levels.(Cassidy & Carroll, 2002) A peak for admissions with a diagnosis of mania in June and July in the British Isles has been described. Women are more likely to experience depressive episodes than mania (men experience both phases with equal frequency) and rapid cycling is more common in females. Mania may be induced in vulnerable people by lack of sleep, crossing many time zones during travel, and shift work.

Bipolar¹³⁷⁸ (BP) v unipolar (UP)

Mania and depression can occur at different times in the same person. Less commonly, they more occur simultaneously in the same person. Sims (2003, p. 313) points out that the opposite of either 'pole' is not mania (for depression) or depression (for mania), but 'freedom from morbid emotion'. Many patients have recurrent attacks of depression only¹³⁷⁹, less commonly there is bipolar affective disorder. They may have euthymic (normal mood) periods between attacks. Less common are chronic depression, chronic mania (said by some to be rare today but one report of hospitalised cases of mania found that 13% were chronic), and so-called rapid cyclers¹³⁸⁰.

Cycling

Rapid cycling, which is more common in females, is present when there are at least 4 episodes/year
Ultra-rapid cycling is when attacks occur every so many weeks to several days¹³⁸¹
Ultra-ultra-rapid (ultradian cycling) is when attacks are of less than 24 hours duration (or several episodes daily)
Continuous cycling when there is no sustained period of stable mood.

Bipolar I disorder prospective study (Solomon ea, 2009)

N = 219; median follow-up = 20 years; 1208 mood episodes
 Major depressive episodes = 30.9%

¹³⁷⁵ In practice, it may be very difficult to distinguish between extremes of schizophrenic and manic speech disorder.

¹³⁷⁶ Recovered manics may realise that they have been sick but still believe that the ecstatic phenomena they experienced whilst ill had some special meaning.

¹³⁷⁷ Hypertension, atrial fibrillation, diabetes mellitus, CVA, etc.

¹³⁷⁸ The French psychiatrist Falret delineated '*folie circulaire*' (manic-depressive illness) in 1851. Manic-depressive illness/disorder/psychosis was dropped in favour of BP disorder because it was seen as being too broad a term, often used synonymously with 'affective disorder' and because not all such patients experience psychosis.

¹³⁷⁹ Farren (2008) suggests that most cases of BP are misdiagnosed (often as UP) and that most of these are misdiagnosed 2-3 times.

¹³⁸⁰ Cycling quickly from depression to mania or vice versa; may be induced by tricyclics or hypothyroidism or be idiopathic.

¹³⁸¹ Some authors define it as episodes lasting a day.

Minor depressive episodes = 13%
 Manic episodes = 20.4%
 Hypomanic episodes = 10.4%
 Cycling = 17.3%
 Cycling + mixed state = 7.8%
 Mixed = 0.2%
 All cycling = 25% of episodes

10-country community study (Lee ea, 2010)

A third to two-fifths of those with lifetime and 12-month BP met criteria for rapid cycling
 Rapid cycling BP associated with younger onset of BP, higher persistence, deeper/more impairing depression, more disruption from mania/hypomania, more anxiety disorders, and greater use of health services

Mood changes in ultradian cycling may be confused with the lability of borderline personality disorder.(Dubovsky ea, 2003, p. 458) Rapid cycling has been reported in 10-20% of BP patients. Nwulia ea (2008) found the best predictors of rapid cycling in familial cases of bipolar disorder to be earlier onset of symptoms (18 v 21 years), comorbid anxiety (47% v 26%), and antidepressant-induced mood switching. Variations within the BDNF gene are associated with susceptibility to rapid cycling bipolar disorder.(Green ea, 2006; Müller ea, 2006)

The frequency of attacks often increases with age. The median age of onset for BP is about 29 years, that UP is about 46 years. Early onset of BP is associated with more recurrences, chronic mood symptoms, and functional impairment.(Perlis ea, 2009)

Winokur ea (1993), in a study of consecutive admissions, found that BP patients had an earlier and more acute onset, more total episodes, more familial mania, an excess of males, and more hyperactivity as children, whereas UP patients had more lifetime medical and surgical interventions. A NIMH study (Coryell ea, 2009a) looked BP I and schizoaffective patients who they divided by age at intake into 18-29, 30-44, and over 44 years. Persistence of depressive symptoms increased significantly in the 2 youngest groups. Earlier ages at onset were associated higher depressive morbidity throughout 20 years of follow-up but did not predict changes in symptom persistence. The proportion of weeks spent in episodes of either pole (depression or mania) correlated across follow-up period in all age groups, although correlations were stronger for depressive symptoms and shorter intervals. Regardless of age at onset, the passage of decades in BP is associated with greater predominance of depressive symptoms in 3rd to 5th decades inclusively and earlier age at onset is associated with greater depressive burden.

Bipolar spectrum disorders are associated with an increased premature mortality rate due to general medical illnesses, a consequence perhaps of unhealthy lifestyle, medication, biology, and disparities in health care.(Roshanaei-Moghaddam & Katon, 2009)

Bipolar disorder with and without comorbid panic disorder¹³⁸² may reflect differing frequencies of alleles for catechol-o-methyltransferase (COMT) and the serotonin transporter.(Rotondo ea, 2002) Zhang ea (2009) found that the low activity allele (Met) of rs4680 in COMT may confer risk for BP in the Han population, the authors suggesting further research in Caucasians.

According to Pavuluri ea,(2002) BP is often misdiagnosed as ADHD or oppositional defiant disorder in children. Prepubertal and early adolescent cases present with irritability, rapid cycling, little inter-episode recovery, and high comorbidity with ADHD and oppositional defiant disorder. Adolescent-onset is associated with substance abuse, anxiety, and an episodic course. Both groups, in contrast to adult cases, have elation, mixed episodes, longer episodes, and poor inter-episode recovery. Adolescent-onset may be misdiagnosed as schizophrenia. If a child has both BP and ADHD, the mood should be stabilised before using psychostimulants.

Bowden (2001) suggested that a bipolar diagnosis in patients who are depressed is suggested by a family history of bipolar disorder, a history of spontaneous or drug-induced mood elevation, a higher frequency of

¹³⁸² Toni ea (2008) found that 16% of their sample of DSM-III-R panic disorder and agoraphobia cases had comorbid bipolar II disorder. The comorbid group had an excess of social phobia, OCD, alcohol-related disorders, and separation anxiety during childhood and adolescence and their relatives had an excess of panic disorder and mood disorders (relative to non-comorbid cases). Comorbidity did not affect outcome, probably because the bipolar II disorder was well controlled.

episodes of depression, more time ill, and symptoms that start and end suddenly. According to Smith and Blackwood,(2004) clues to underlying bipolar affective disorder in a patient is depressed include onset before age 25 years, multiple short-lived episodes (< 3 months), racing thoughts whilst depressed, hyperphagia, increase in weight, lethargy or psychomotor slowing, poor or transient response to antidepressant drugs, close relatives with bipolar disorder, multiple relatives with unipolar depression, psychotic features, postpartum onset, mania secondary to antidepressants or ECT, and hyperthymic personality traits. Forty ea (2008) compared major depression and bipolar disorder patients and found psychosis, diurnal mood variance, hypersomnia during depression, and more frequent short episodes of depression to predict bipolarity.

Relative to Australian major depression cases, BP patients had a more equal gender ratio, were more likely to be widowed/separated/divorced, had higher rates of substance abuse/dependence, spent more days out of role, were more likely to be getting medication, and had higher lifetime rates of suicide attempts.(Mitchell ea, 2004)

Bipolar disorder, manic phase, in people with intellectual disability may present as overactivity, aggressiveness, irritability, and undue elation and laughing, or with public masturbation.

In a systematic review and meta-analysis, Beynon ea (2008) found that CBT (in stable patients), group psychoeducation (supported by Colom ea, 2009) and possibly family therapy may be helpful in the prevention of relapse in BP when used as adjuncts to pharmacological maintenance treatments. However, Lynch ea (2010), in a meta-analytic review, found no evidence that CBT prevented relapse in BP. Castle ea (2010) found that group-based psychosocial intervention did reduce relapse risk in BP, although there may have been problems of expectation among patients and clinicians ('unmasked') who conducted follow-up telephone calls and 'clustering effects' may have occurred between and within groups.

Depression and cancer

If a person becomes depressed in middle age, especially if it is for the first time and if no precipitant can be found, should be rigorously investigated to exclude physical disease. One theory of the connection between cancer and depression is that tumour protein excites antibody formation, the latter then interfering with 5-HT transmission.

Affective disorders may be an early precursor of clinical cancer, especially with cancer of the pancreas (more than with gastric cancer). Depression may predate physical clues to cancer by many months. Depression may persist despite successful cancer treatment. One example of a successful programme for treating depression in people with cancer involves nurse-delivered education about depression and its treatment (including antidepressant medication), help with coping strategies (problem-solving), and communicating with the oncologist and GP.(Strong ea, 2008)

Seasonal affective disorder (SAD)

SAD is officially one of the affective disorders, although there have been many detractors for its acceptance as a discrete entity.(e.g. Kendell, 1993; Goodwin, 2004; Baldwin & Hirschfeld, 2005, p. 29) Kendell (1993) pointed to a need for prospective studies on less selective groups and the possibility that light therapy may act as a placebo. Other criticisms include the inclusion of mildly depressed outpatients, the difficulties of establishing an adequate placebo group, low numbers in light therapy studies, lack of comparison with established treatments, uncontrolled studies, apparent seasonality (non-seasonal episodes on follow-up), and the finding of peaks in all seasons, including spring-summer depression. Levitan (2007) states that subsyndromal SAD, a mild version of the disorder, affects 'many adults' and opines that seasonality could be a dimensional rather than a categorical/discrete syndrome. DSM-IV-TR views a *seasonal pattern* as an additional specifier of recurrent major depressive disorder or bipolar I or II disorders. DSM-IV-TR criteria for seasonal pattern specifier excludes cases where there is an obvious seasonal-related psychosocial stressor, such as not being employed during the winter months.

Classically the patient becomes depressed in autumn or winter and the condition remits by the following spring or summer over at least two years (reversed in the Southern Hemisphere). Schlager ea (1993) found that healthy women, but not men, had more symptoms (anxiety, somatisation, depression) in the two weeks before testing in winter than at other times. They used the Hopkins Symptom Checklist. Follow up of patients has shown considerable variability in the sense of change of season during which depression is experienced and changes in both directions from SAD to non-SAD. According to one relatively small

study, recent negative life events and poor social support may increase seasonality in mood disorder.(Michalak ea, 2003)

Attempts to examine the photoperiod (shorter daily length of exposure to natural or artificial light increases SAD rates) or latitude (higher rates further north) theories of SAD have provided major challenges for researchers.(Levitan, 2007) For example, Levitt and Boyle (2002) were unable to confirm a relationship between latitude and SAD rates in Ontario, Canada.

SAD is said to affect almost 10% of Alaskans, where young and female cases are in the majority (although, young male Alaskan natives have a very high suicide rate: Gessner, 1997). Affected subjects are reactive to changes in some environmental factor, e.g. climate, latitude or environmental light. It may be related to hibernation in animals. Relatives seem to have high rates of alcoholism. It may also simply be an exaggeration of normal familial seasonal changes in mood.

Goikolea ea (2007) followed up 125 cases of bipolar I and II patients for 10 years. 25.5% were considered seasonal. A seasonal pattern was associated predominantly bipolar II disorder, depressive onset and mainly depressive polarity. Demography and severity indicators¹³⁸³ did not distinguish seasonal from non-seasonal cases.

Allen ea (1993), using the family history method, found that the genetic loading for mood disorders was similar for both SAD and non-seasonal mood disorders. N-acetyl-5-methoxytryptamine (melatonin) is a pineal hormone derived from 5-HT. Melatonin secretion was reported in the past to be normal in SAD. However, nocturnal plasma melatonin and mean 24-hour concentration has also been reported as being reduced in depression (Rabe-Jablonska and Syzmanska [2001] found mean melatonin concentration in depression to be *higher* than normal at some points during the night). As well as this, amplitudes of melatonin circadian rhythm may be smaller than usual whilst people remain depressed.(Sou ete ea, 1989) Most people with low melatonin levels are not depressed.(Schulz, 2007) Antidepressants are not consistent in their effects on melatonin, e.g. fluoxetine has been found to reduce and both fluvoxamine and TCAs have been reported to increase melatonin levels in both patients and controls. It has also been reported that SAD is associated with enhanced sensitivity to melatonin suppression by bright light in winter but not in summer.¹³⁸⁴

M-chlorophenylpiperazine (m-CPP), a 5-HT receptor agonist, causes euphoria or activation during a depressive episode in SAD patients but not in non-SAD cases in controlled *but* different studies.(Levitan, 2007) The binding potential of the serotonin transporter (5-HTT) varies with season.(Praschak-Rieder ea, 2008) The short allele polymorphism for the 5-HTT was found to be more common in SAD cases than in healthy people. Patients with two long alleles may have milder symptoms than if they had at least one short allele. Other research found no support for a role of this short variant in susceptibility to SAD but found modest evidence for an effect on seasonality.(Johansson ea, 2003) However, the literature in this area is at present discrepant.

Bright, full-spectrum lights are used in treatment. Light is known to have a ‘profound placebo component’ (Lewy ea, 2007) and methodological problems bedevil research in this area.(Anonymous, 2009)The finding that green light is better than red light and similar to white light has been interpreted to support the hypothesis that retinal photoreceptors mediate the antidepressant response in SAD. The depression may be characterised by weight gain, hypersomnia, overeating and carbohydrate craving. There may be less suicidal ideation and early morning worsening of mood than in non-seasonal mood disorder patients. The depression may improve by travelling toward the Equator and worsen with proximity to the Poles. Patients with SAD have recovered with phototherapy but relapsed when the light was withdrawn. Early guidelines for winter depression suggested that eyes should be exposed to full visible light. The light should be sufficiently intense and the treatment sufficiently prolonged (e.g. 2,500 lux for at least 2 hours). Treatment is given daily throughout the seasonal period of risk (early autumn to early spring). Light therapy is therefore inconvenient but worthwhile for many sufferers. Portable bright light visors may reduce the need to sit in front of a light for long periods. There is evidence that the timing of light therapy is not crucial. However, use close to bedtime may be too alerting. The eyes may become slightly irritated or reddened initially but this is generally transient.

¹³⁸³ I.e. psychosis, admission to hospital, or suicidality.

¹³⁸⁴ According to Nurnberger ea(2000), euthymic BP I patients relative to euthymic UP cases may have reduced melatonin if exposed to light and peak melatonin levels during dark nights.

Bright white light is no better than dim light in non-seasonal depression (and any effect may not last: Martiny ea, 2006), and extra light given during the day is just as good as extra light during the hours of darkness. Light therapy non-responders tend to be melancholic¹³⁸⁵. Because rapid tryptophan depletion reverses gains from bright light therapy, serotonergic mechanisms may be involved in its therapeutic action.(Neylan ea, 2003, p. 985)

Dawn simulation¹³⁸⁶ may be at least as effective as bright light treatment.(Avery ea, 2001)

Negative air ion concentration tends to be higher in summer than winter and in humid than dry environments. Negative air ion generation, used at home, is currently being studied for winter depression.(Howland & Thase, 2002) However, it may also be effective for chronic non-seasonal depression, as may bright light be.(Goel ea, 2005) Dawn simulation and negative air ion generation were effective for SAD in the Terman and Terman study.(2006)

A morning walk has been reported to be effective in SAD,(Graw ea, 1991) as have cooling and dark glasses in patients with regular summer onset of depression.(Wehr ea, 1987) Antidepressants are effective in SAD, probably as effective as light treatment.(Lam ea, 2006) Mood and appetite changes in SAD may respond to fenfluramine.(O'Rourke ea, 1989) Partial sleep deprivation¹³⁸⁷ plus bright light treatment might boost the effects of antidepressant drug treatment.(Coryell, 2008, p. 517)

One review (Anonymous, 2009) suggests that mild/moderate SAD may be treated with early morning bright light (using a light box or dawn simulation) with or without CBT or medication; severe SAD requires treatment with antidepressant medication with/without light therapy/CBT.

Dexamethasone¹³⁸⁸ suppression test (DST)

Almost half of primary depressives have increased cortisol levels and there may be increased adrenal gland size. Failure of exogenous dexamethasone to suppress endogenous cortisol was reported to be of value in differentiating endogenous or biological depression from other types of depression. Plasma cortisol levels fall in the second half of the day in healthy people but were noticed to remain high in some depressives. Also, non-suppression increases with age, especially in the elderly. Carroll (1981) claimed an overall specificity of 96% and a sensitivity of 43% for the DST, i.e. a positive DST (non-suppression) can be used with high confidence to support a diagnosis of melancholia, but a negative DST will not necessarily rule it out. However, the DST had a poor specificity in a group admitted to an in-patient crisis unit when it was used to detect TCA responders. It was also unhelpful in predicting response to ECT. Increased plasma cortisol concentrations may be simply a non-specific symptom of psychosis or of acute distress.(Tyrer & Silk, 2008, p. 4) A childhood neurotic symptom pattern of excess anxiety, agitation, initial insomnia, aggression and stressful events was reported to be associated with a positive (non-suppression of cortisol) DST by Abou-Saleh (1985) but others found no significant association between depression in children and DST results.(Tyrer ea, 1991) Keane and Soni (1992) found the DST to be valueless as a diagnostic tool among the intellectually disabled in the community. Manic patients have a high cortisol level. Tricyclic withdrawal interferes with the DST. A list of situations associated with positive and negative DST results is to be found in the box. The DST might be useful in determining the need for maintenance therapy after successful treatment for depression. Peselow ea (1989) found that a positive DST predicted a response to antidepressants rather than to placebo. Bowie ea (1987) found that a persistent suppression of the DST during the index illness was a predictor of good prognosis. In their literature meta-analysis, Ribeiro ea (1993) found that baseline DST results did not provide prognostic information but that if cortisol remained non-suppressed after treatment there was a good chance of a poor outcome.

Depressed patients do not become cushingoid despite evidence for increased glucocorticoid levels. Dinan (1994) suggests that this might be due to reduced glucocorticoid receptor activity: perhaps increased CRF leads to downregulation of pituitary CRF receptors and decreased ACTH response to CRF¹³⁸⁹. Finally, it should be noted that dexamethasone itself may have some antidepressant properties!(Arana ea, 1995)

¹³⁸⁵ Retardation, worse in the morning, suicidal, depersonalised, anxious, early and late insomnia, anorexic, guilt.

¹³⁸⁶ Low intensity light that gradually increases illuminance before patient awakens.

¹³⁸⁷ Sleep deprivation (wake) therapy can involve once-off or repeated deprivation of all night sleep (total), partial (often second half of night), or selective (REM deprivation) parts of sleep. Total sleep deprivation may be the most beneficial, irrespective of what component (REM or N-REM) sleep is lost most.(Hajak & Popp, 2008, p. 79)

¹³⁸⁸ Dexamethasone is used for suppression because (unlike prednisolone) it does not show up as cortisol in a radioimmunoassay.

¹³⁸⁹ Depressives who are non-suppressors in the DST have higher CSF CRF levels than do depressed people who have a normal DST. This may result from excess CNS CRF secretion: actions of CRF at various brain sites could account for various manifestations of

'False'* positive and negative DST results

'False' positives

BZDs, anticonvulsants**, barbiturates, reserpine, α -methyl DOPA, methadone, morphine, spironolactone, cyproheptadine, alcohol, excess caffeine

Diabetes mellitus, dementia, cerebral tumour, cardiac failure, Cushing's disease, dehydration, pregnancy, any acute medical illness/trauma (systemic infection and hepatic disease), weight loss, sleep deprivation

Anorexia (36-100%)*** or bulimia (35-67%) nervosa, mania,(0-40%) schizophrenia,(0-20%) panic disorder, (25%)**** borderline personality disorder¹³⁹⁰, (8%) OCD, (2%)

Normals (4-27%)

'False' negatives

Corticosteroids, high-dose benzodiazepines, dextroamphetamine, Addison's disease, hypopituitarism

*False in the sense that one assumes for argument's sake that the test is only valid in depression! **Carbamazepine accelerates metabolism of dexamethasone and may give a false positive DST in patients being investigated for possible Cushing's syndrome.(Ma ea, 2005) ***Compare with 45% in melancholia. ****Low percentages in anxiety disorders and bereavement would be an argument as a non-specific stress response explanation. Generalised anxiety patients often have low normal baseline cortisol levels but may fail to show suppression during the DST and non-suppression may diminish as the condition responds to treatment.(Tiller ea, 1988)

The *combined dexamethasone/CRH test (dex/CRH)*¹³⁹¹ may have better sensitivity for detecting small changes in HPA axis function, the result being abnormal in twice as many major depressives as have an abnormal DST. Also, at-risk first-degree relatives of affective disorder cases have higher cortisol and ACTH responses than controls but less than people suffering major depression.(Holsboer ea, 1995) This may represent trait vulnerability. Bipolar (BP) patients may also have an elevated cortisol response to dex/CRH that fails to normalise during clinical remission¹³⁹²; this finding has also been suggested to represent a trait marker for BP.(Watson ea, 2004) Elsewhere Watson ea (2002) suggest that HPA axis dysfunction may be a manifestation of acute but not chronic depression.

Nelson's syndrome (low corticosteroid and high ACTH levels)¹³⁹³ patients are not noted for being depressed.(Kelly ea, 1980) Does this point the finger at cortisol rather than ACTH as of aetiological importance in depression?

Pregnancy

One should never assume that a woman is sexually inactive because she has a mental disorder, and whilst unplanned pregnancy is very common in the community it is especially frequent likely if the woman is mentally ill.(Abel, 2007, p. 637) A Danish study of psychiatric readmission (Munk-Olsen ea, 2009) found that mothers with a psychiatric disorder were less likely to be readmitted¹³⁹⁴ compared with childless women with a psychiatric disorder; that the first postpartum month is associated with increased risk of readmission; and that bipolar disorder carries a particularly high risk of postpartum readmission. Findings of somewhat higher rates of gestational hypertension/pre-eclampsia in women taking SSRIs do not discriminate the possible causal effects of treatment from the mood disorder being treated.(Toh ea, 2009)

depression. Reduced density of frontal cortical CRF receptors has been found in completed suicides.(Nemeroff ea, 1988) Animal and human research suggests that early abuse and neglect may lead to persistent HPA axis/extra-hypothalamic CRF overactivity, sensitising the patient and increasing the risk of later depression.(Nemeroff & Gutman, 2002, p. 108)

¹³⁹⁰ See Carrasco ea (2007).

¹³⁹¹ 1.5 mg dexamethasone orally at 11 pm. 100 micrograms human CRF (CRH) IV at 3 pm next day. HPA axis dysfunction shows up as **increased** release of ACTH and cortisol relative to control cases. HPA axis dysfunction normalises before full response to treatment of depression.

¹³⁹² BP patients had increased cortisol response to combined dexamethasone/CRH test compared with controls, a similar response being found in remitted and non-remitted cases.

¹³⁹³ **Nelson's syndrome** was more common when bilateral adrenalectomy was used to treat Cushing's syndrome.(Nelson ea, 1960) The post-operative lack of cortisol removed the normal negative feedback on the pituitary and allowed any pre-existing pituitary adenoma to grow unchecked. Both ACTH and MSH levels are increased. Typical clinical features include hyperpigmentation and muscle weakness.

¹³⁹⁴ Of course, mothers may be reluctant to go into hospital if they have children at home.

Maternal death related to pregnancy: 536,000 women die each year, 99% of these in the developing world, from complications of pregnancy and childbirth.(Obaid, 2007) A report from the Royal College of Obstetricians and Gynaecologists in the UK (Lewis & CEMACH, 2004; Anonymous, 2004a) found that 40% of maternal deaths were attributable to indirect causes with depression and suicide a particular concern. 35% of the women studied were obese, higher than among women in general. Obesity may act via lifestyle factors such as smoking and a sedentary existence.

Depression during pregnancy is not uncommon (about 10% during any trimester), contrary to popular belief (Kitamura ea, 1993; Dietz ea, 2007), although not all research agrees.(Vesga-López ea, 2008) Major and minor depression are equally common in gravid and non-gravid women.(Burt & Hendrick, 2003, p. 1516) Women with a prior history of recurrent affective disorder who stop their medication are especially at high risk for relapse during pregnancy. There may be an association between early gestational depression and psychosocial factors, such as first or unwanted pregnancy, poor marital relationship, unsatisfactory living conditions, less maternal care in own childhood, and having remarried. Parry ea (2008) found that night-time plasma melatonin levels, especially during the morning hours, were relatively low in depressed pregnant women but relatively increased in depressed postpartum women; also, the timing of melatonin production was advanced in pregnant women with a personal or family history of depression. Suicide (and deliberate self-harm) is rare during pregnancy,(Appelby & Turnbull, 1995) although it may have been more common in the past, although teenage and single mothers may represent high-risk groups.

It should also be noted that obsessive-compulsive disorder (OCD) often worsens in pregnancy and/or the puerperium.(Neziroglu ea, 1992) Evidence as to whether a first episode is commoner during pregnancy is conflicting. There may be obsessions of infanticide (which may be extreme, e.g. beheading) but the clinician must still encourage the mother to interact with her baby. Panic disorder may be exacerbated during the puerperium, and Cohen ea (1994) suggest that this possibility may be heightened by not treating panic disorder during pregnancy.

The **postpartum/maternity blues/reactivity** affects over 50% of mothers on days 3-5 postpartum and is generally resolved by day 10. There are transient labile emotions (heightened responsiveness to good and bad stimuli), tearfulness, mild hypochondriasis, irritability, and anxiety. It can occur with hospital or home deliveries.

Aetiology (unclear)

Primigravida

History of third trimester depression or premenstrual dysphoria

Psychological, e.g. no longer pregnant, responsible for baby, effects of having a baby on relations with other adults, including the father of the child

Lack of sleep¹³⁹⁵ and fatigue

Psychoanalysts stressed unresolved feelings towards ones own mother from childhood, sexual identity difficulties, and re-experiencing of earlier sibling rivalry (such postulations could equally apply to problems during pregnancy or other postnatal psychiatric difficulties

Fall in progesterone levels

Increase in platelet beta-adrenoreceptors before and during the blues (Metz, 1983)

Management consists of waiting, reassuring, and forewarning. Particularly severe cases should prompt a search for another psychiatric disorder.

Postnatal (postpartum) depression (PND) occurs after at least 10% of births¹³⁹⁶,(O'Shea, 2000e; Wisner ea, 2002; Crotty & Sheehan, 2004) and a significant minority of such cases are a continuation of depression from pregnancy.(Watson ea, 1984) Sixty percent are fully recovered inside a year. Others may show some level of chronicity. Mood varies from day to day. There is anxiety¹³⁹⁷, irritability, tiredness, despondency, and initial insomnia. Murray ea (1995) found no symptomatic difference between early versus late PND or

¹³⁹⁵ Debate exists as to whether sleep disruption is more important before or after delivery; the same applies to night-time labour.

¹³⁹⁶ Cooper ea (2007) are sceptical about the differences between PND and non-PND depressive episodes, e.g. reduced early morning wakening could be due to having a new baby! Young ea (2010, p. 635) and Brockington (2010, p. 722) suggest that there is little difference between the prevalence of postnatal depression and depression in non-gravid women.

¹³⁹⁷ High levels of anxiety early on may predict PND.(Teissedre & Chabol, 2003)

between PND and non-PND depression. PND is more common with a past history of psychiatric disorder or high interpersonal sensitivity or neuroticism,(Boyce ea, 1991) young age, early postnatal blues (debatable: Miller & Rukstalis, 1999), delivery by forceps/vacuum/caesarean section (cs),¹³⁹⁸ poor marital relationship (Patel ea, 2004) or single status, severe life event in the previous year,(Marks ea, 1991), no social supports, in-law difficulties,(Lee ea, 2004) ambivalence about the pregnancy, and perinatal death. Murray ea (1995) found that women with PND had poor relationships with their own mothers and occupational instability. Depressed women without PND on the other hand had at least three children and manual employment that they disliked. Vigod ea (2010) conducted a systematic review and reported that mothers of preterm infants are at increased risk of depression compared with mothers of term infants in the immediate postpartum period; risk continued throughout the first postpartum year for mothers of very low birth weight infants. High scores on the *Edinburgh Postnatal Depression Scale* at 6 weeks are associated with single marital status, unemployment, unplanned pregnancy, public patient status, and bottle-feeding. There is evidence from Nigeria and South Asia that pre- and post-natal neuroticism may be largely caused by psychosocial factors (Aderibigbe ea, 1993; Patel ea, 2004) and psychological vulnerability to PND may be similar to that for depression at any other time.(Jones ea, 2010)

Maes ea (2001) found that plasma tryptophan falls at term and after delivery but bore no relationship to the risk for PND. High-expression 5-HT transporter genotypes may be a risk factor for depressive symptoms following childbirth.(Sanjuan ea, 2008)

There is no evidence to incriminate progesterone withdrawal in postpartum depression – despite this, and lack of evidence of effectiveness, progesterone is often prescribed¹³⁹⁹. A particularly low evening serum cortisol concentration just after delivery may be more common in PND cases. There is a suggestion that thyroid antibody positive status may increase the risk for this disorder,(Harris, 1994) but giving thyroxine does not prevent PND in such cases.(Harris ea, 2002) There is preliminary evidence that increased levels of placental corticotropin-releasing hormone (pCRH)¹⁴⁰⁰ at 25 weeks gestation predicts postpartum depression.(Yim ea, 2009)

In a study of 483 women, the prevalence, incidence, and nature of non-psychotic psychiatric disorder in the twelve months following delivery failed to distinguish it from such disorders arising at other times,(Cooper, ea, 1988) although others have found that women with a past history of non-PND depression who now experience an episode postnatally may revert to their original pattern whereas women who had their first episode of depression after delivery may be at risk only for postnatal recurrences.(Cooper & Murray, 1995) It has been suggested that the closer the onset of depression to the birth the greater the likelihood of neuroendocrine factors being operative. Management involves a package of counselling, psychotherapy, family work, chemotherapy (e.g. fluoxetine), and practical assistance. Evidence has been reported for efficacy in PND for cognitive behaviour therapy¹⁴⁰¹,(CBT: Appleby ea, 1997; Chabrol ea, 2002) interpersonal therapy,(O’Hara ea, 2000) and non-directive counselling.(Holden ea, 1989) Cooper ea,(2003) found that psychodynamic¹⁴⁰² produced a decrease in depression at 4.5 months, but that no of the active treatments were superior to the control intervention at 9 months. As far as prevention is concerned, Dennis (2005) concluded that diverse psychosocial and psychological interventions do not significantly reduce the number of women developing PND, but that there is some support for the prophylactic efficacy of intensive support from a health professional. There is evidence from Canada (Dennis ea, 2009) of a prophylactic effect of telephone-delivered support delivered by people with a self-reported history of and recovery from postnatal depression for women at risk¹⁴⁰³ of postnatal depression.

Transdermal oestrogen (e.g. 17 β oestradiol) may be worth trying in severe cases.(Gregoire ea, 1996)

However, the efficacy of oestrogen without a co-prescribed antidepressant remains controversial.(Wisner ea, 2002) It has been suggested that breast feeding might be unwise because of the associated

¹³⁹⁸ Patel ea (2005) did not find support for this contention.

¹³⁹⁹ In fact, there is more evidence that progesterone can make depression worse in these patients.(Lawrie ea, 1998)

¹⁴⁰⁰ In contrast to the negative feedback of cortisol on the HPA axis cortisol *stimulates* placental CRH production. Therefore, pCRH levels in mother’s plasma increase exponentially throughout pregnancy. In fact pCRH levels reach those of hypothalamic CRH in the median eminence during acute stress. Removal of the placenta at delivery leads to a precipitous drop in pCRH levels. This CRH withdrawal state results in short-lived suppression of hypothalamic CRH release and dysregulation of the HPA axis.

¹⁴⁰¹ Treatment based on CBT has been delivered by community health workers in resource-poor settings (Rahman ea, 2008; Patel & Kirkwood, 2008) and by health visitors in England.(Morrell ea, 2009)

¹⁴⁰² But not routine primary care, non-directive counselling, or CBT.

¹⁴⁰³ Identified using the *Edinburgh Postnatal Depression Scale*.

hyperprolactinaemia. Recognition is important in order to reduce chronicity. The woman must be allowed to ventilate her feelings, e.g. guilt, anxiety about baby, suicidal or homicidal thoughts, loss of interest in sex, fears that the baby might not be hers, or fears that the child is deformed. There is evidence for adverse emotional and cognitive effects on the infant. (Murray ea, 1991; Patel ea, 2004)

'Neurotic disorders' other than depression may occur during the puerperium, e.g. phobias (including agoraphobia), anxiety, or OCD.

Postnatal psychotic depression complicates 0.2% of births¹⁴⁰⁴. Suicide and infanticide are real possibilities. The risk of recurrence in another puerperium is at least 20%, higher (40%) if there is a history of episodes of affective illness unrelated to childbirth. At least 50% experience a later non-puerperal depressive episode. The following factors may be associated with an increased risk of admission to a psychiatric unit with puerperal psychosis: the first 30 days postpartum, primiparae, single marital status, cs, perinatal death, and a history of BAD¹⁴⁰⁵ or schizoaffective disorder. (Blackmore ea, 2006) However, while hospitalisation for psychiatric morbidity before delivery is common in such cases, (Harlow ea, 2007) puerperal psychosis can occur in women with no psychiatric history. It was suggested that postpartum psychosis may be associated with supersensitivity of DA receptors, perhaps triggered by a sharp fall in oestrogen levels following parturition, but this has not been confirmed.¹⁴⁰⁶

Symptoms, which usually commence within two weeks of delivery, include guilt, despair, psychomotor retardation or agitation, perplexity, lability of affect and disorientation. Management involves admission of the mother and if at all possible her child, careful observation, ECT if indicated, and antidepressants. Mixed affective state may carry a higher suicide risk than postnatal psychotic depression. The requirement for mother and baby unit beds has been estimated at 8/million total population.

Special risks for infanticide¹⁴⁰⁷ include young motherhood and poor education. The infanticide rate in the USA was at least 9/100,000 live births during the period 1988-91. The Irish forensic dimension has been explored by Mulryan ea. (2002) A marked decrease in the number of women admitted to Ireland's only 'special' hospital on charges or conviction for infanticide may reflect altered judicial attitudes. The authors suggest that the barriers to the movement of pregnant women to Britain during World War II may explain a dramatic increase in the number of infanticide cases appearing before the Irish Central Criminal Court between 1940 and 1946. (Mulryan ea, 2002)

It should be noted that women with a history of psychotic disorder may have an increased risk of stillbirth and neonatal death. (Howard ea, 2003) They should be the focus of optimal antenatal care, including counselling on smoking and substance misuse.

Treatment strategies

Treatment options include supportive psychotherapy¹⁴⁰⁸, cognitive-behaviour or interpersonal therapy (when available), cognitive remediation therapy¹⁴⁰⁹, marital therapy (especially if there is accompanying marital distress) environmental manipulation (e.g. re-housing), assertiveness training, prompting, shaping, general measures (e.g. feeding), sleep deprivation¹⁴¹⁰ (in depressives), stereotactic psychosurgery (rarely),

¹⁴⁰⁴ Are postpartum psychoses getting less common (Tschinkel ea, 2007) or is what that are included under this rubric shrinking?

¹⁴⁰⁵ According to Yurgelun-Todd (2007, p. 146) 30% of women with postnatal psychosis will be diagnosed as having bipolar disorder, and 30% of women with BAD will receive a diagnosis of postnatal psychosis whereas only 1 in 1,000 women in the general population experience postnatal psychosis.

¹⁴⁰⁶ Depressive symptoms in women taking anovulant pills were associated with the amount of oestrogen relative to progesterone. (Hall ea, 1980)

¹⁴⁰⁷ **Infanticide** was employed for centuries in China as a means of population control. Today, infanticide, especially in the first days after the birth, may indicate social reasons (the unwanted and disguised pregnancy) rather than psychiatric disorder. In the US, white female infants have greatest risk of all white females of being murdered. (Malmquist, 2006, p. 4)

¹⁴⁰⁸ Among the approaches used are psychoeducation, dealing with stigma/low self-esteem/interpersonal problems/legal difficulties/social and occupational consequences. Miklowitz (2008) looked at 18 trials of individual and group psychoeducation, systematic care, family therapy, and interpersonal or cognitive behavioural therapy as adjuncts in bipolar patients and found that they improved symptoms and function over 2 years; emphasis on medication compliance and recognition of early mood changes had stronger effects on mania, whereas emphasis on cognitive and interpersonal coping strategies had stronger effects on depression.

¹⁴⁰⁹ Elgamal ea (2007) improved cognition in 12 cases of major depression with computerized cognitive remediation (targeted, repetitive) exercises despite no change in depression scores.

¹⁴¹⁰ Wu ea (2009) used *chronotherapeutic augmentation* (sleep deprivation, bright light therapy, and sleep phase advance) in 49 outpatients with BP depression (measured with HRSD) and reported a rapid and sustained antidepressant response. Two patients experienced hypomania which resolved spontaneously within 24 hours.

ECT, repetitive transcranial magnetic stimulation¹⁴¹¹, antidepressants¹⁴¹², 'anti-manics'¹⁴¹³, light therapy, dark therapy¹⁴¹⁴, and, rarely, psychosurgery for depression. Except for the mildest cases (where 'watchful waiting' may be appropriate) the earlier treatment is instituted the better. Immediate response to antidepressant therapy may constitute a placebo effect; such cases are prone to early relapse. Many people imagine antidepressants to be non-efficacious or addictive, and many have magical expectations of counselling. Apart from giving medication, it is important to address any persistent dysphoria, low self-esteem, or confounding psychosocial issues. Arguably, physical exercise, such as running, may alleviate less severe forms of depression and anxiety (Greist ea, 1979; Mather ea, 2002), but is this due to exercise, lack of inactivity, or a third unknown factor?(Wilkinson, 2008, p. 248; De Moor ea, 2008) Also, exercise was not effective in one study in preventing depression in older adults in one study.(Walker ea, 2010) In general, cognitive therapy may be less effective for severe depression or for those cases with an abnormal EEG profile. Four different psychotherapeutic strategies for depression are summarised in the box. Couple therapy may help in cases where relapse appears to be precipitated by having a critical partner. According to Keck,(2004) psychoeducation may be better at preventing manic than depressive relapses in bipolar disorder, with the opposite effect for family-focused therapy.

Five approaches to psychotherapy in depression

*Psychodynamic*¹⁴¹⁵ (e.g. Freud, Kohut). Ego regresses due to losses in childhood. Therapist must understand past, defences, ego distortions, superego defects, and provide role model and permit catharsis. Aim at personality change. Employ expression/reflection. Be empathic. Analyse/explore transference/resistance. Confront defences. Clarify ego/superego distortions. Utilise therapeutic alliance for benign dependence/empathic understanding. Treat individual in confidence. Apart from emergencies, exclude others.

Interpersonal (e.g. Sullivan, Klerman). Unsatisfactory interpersonal (IP) relations/bonds. Aim to solve current IP problems, reduce stress, and improve communication skills. Aim to relieve symptoms. Clarify maladaptive relationships and learn new ones via communication/social skills training. Didactic teaching re illness. Explore/prescribe. Use positive relationship. No interpretation of transference. Active therapist: influence/advocacy. Use partner and his/her role in patient's disposition to depression. Look at illness effects on relationship. Interpersonal psychotherapy is an alternative to medication in the depressed breast-feeding mother.

Cognitive (e.g. Beck). Distorted thinking due to learned negative views. Change target thoughts. Modify false assumptions. Increase self-control over thinking patterns¹⁴¹⁶. Aim at symptomatic relief¹⁴¹⁷. Cognitive-behavioural approach (CBT): record/monitor cognitions/correct distorted themes using logic and by testing them in vivo/provide alternative thought content/give homework assignments/educate and shape/use positive relationship/avoid transference/and collaborative empiricism for joint logical task. Use partner as objective reporter/couples therapy if relationship disturbed/thoughts sustained by relationship.

Behavioural. Such approaches are based on learning theory, e.g. use of operant conditioning to develop a structured daily action plan. Ekers ea (2008) conducted a meta-analysis of 17 RCTs (1109 subjects) and found pure behavioural therapy to be effective with equal outcomes compared to CBT.

Supportive (L. to carry). Commonest approach. Here and now. Adjunctive. Avoid transference. Didactic, empathic, active. Draws on many schools of psychotherapy as needed. Can be used with any other suitable

¹⁴¹¹ No better than sham treatment according to Mogg ea.(2008)

¹⁴¹² Patients with significant medical illness are more prone to adverse effects and those with secondary major depression may respond to relatively low doses.(Hanretta & Fogel, 2003)

¹⁴¹³ E.g. neuroleptics, lithium, anticonvulsants for the treatment or prevention of mania or antidepressants for the treatment or prophylaxis of depression.

¹⁴¹⁴ Barbini ea (2005) report that extended darkness may reduce manic symptoms when given early in an episode (pilot study).

¹⁴¹⁵ Taylor (2008) argues that whilst the effects of CBT may be relatively acute, those of short-term psychodynamic therapies may continue to increase following treatment, and longer-term psychodynamic approaches may have wide positive effects on personal function as well as improving symptoms of depression.

¹⁴¹⁶ Mindfulness-based cognitive therapy(Teasdale et al, 2002) aims to prevent relapse of depression by instilling meta-cognitive awareness (a normal person knows that his thoughts and feelings are products of his mind and not objective truths about the self).

¹⁴¹⁷ Fournier ea (2008) found that paroxetine worked faster than cognitive therapy for depressives with personal disorder and a meta-analysis found only a small effect for CBT in the management of major depression.

measure, e.g. environmental manipulation. Partner and others (e.g. housing authority, bank manager) may be approached (with permission).

Luty ea (2007) found interpersonal (IPT) and cognitive-behavioural therapies effective in depressed outpatients, with the latter being more effective than IPT in cases with MADRS score above 30 ('severe'). Therapist-delivered CBT for depression on the internet seemed to be effective and to remain beneficial over 8 months in one RCT based in primary care. (Kessler ea, 2009) Psychotherapy may have a role in preventing depression. (Cuijpers ea, 2008¹⁴¹⁸)

Interpersonal and social rhythm therapy may improve occupational functioning in BP I patients. (Frank ea, 2008a)

Cuijpers ea (2010) chose RCTs of the use of psychotherapy in the treatment of adult depression on the basis of 8 quality criteria (e.g. 2 independent coders and participants meeting diagnostic criteria). The results of their meta-analysis suggested that while psychotherapy had significant effects such effects are much smaller than was previously understood.

Whether to start treatment with a TCA (cheap, toxic in overdose, etc) or an SSRI (expensive, sexual side effects) is controversial¹⁴¹⁹ (Harrison & Geddes, 1995) and the decision should be based on an understanding of a number of variable such as economics, overdose potential, treatment history, and physical status. Cipriani ea (2009) compared the efficacy and acceptability of twelve 'new-generation' antidepressants in a meta-analysis: mirtazapine, escitalopram, venlafaxine and sertraline were more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and, the least efficacious, reboxetine. The authors suggest starting with sertraline (Lustral, Sertral) when treating moderate/severe major depression in adults because it had the best balance between efficacy, acceptability, and cost. Uher ea (2009) found that escitalopram improves observed mood and cognitive symptoms more than does nortriptyline whereas the opposite applies to neurovegetative symptoms. (see also Uher ea, 2010)

The common method of defining a response on the basis of a 50% reduction in Hamilton score does not necessarily mean that the patient is clinically recovered¹⁴²⁰; the same criticism applies to Y-BOCS scores and OCD. Baldwin ea (2002, p. 75) point out that older people are more likely to overdose with analgesics than with antidepressants.

Past personal response to a particular antidepressant or a family history of such a response is a good argument for using it again during the index episode. It has been suggested that patients with the lowest pre-treatment evening TSH secretion have a low response rate to antidepressant drug therapy. MAOIs may be chosen (for responsible of supervised patients who fail trials of other drugs) because of a reverse neurovegetative symptom cluster – hyperphagia, anergy, and psychomotor retardation - although patients with classic melancholia may also respond to this class of drug. Howland & Thase (2002) suggest that MAOIs are effective in about 50% of depressions resistant to other drugs.

The old idea of reducing a therapeutic dose to a maintenance or prophylactic one after symptoms remit was mistaken: the patient should be kept on the dose that worked for at least 6 months. No one knows how long an individual episode will last. It is the author's practice to *aim at* 2 years treatment, followed by a slow taper if history and symptoms/function suggest it is safe to do so. Not everyone who needs long term antidepressant treatment gets it or receives it for long enough. (Holma ea, 2008) Depression is a long term illness. (Montgomery, 1994). Geddes ea (2003) conducted a systematic review of 31 randomised trials of continuation antidepressant drug therapy and found that whilst treatment effects seemed to last over 3 years, most trials were only a year in duration; average relapse rate on drug therapy was 18%, 41% on placebo; and 18% of active drug treatment cases stopped the drug, 15% on placebo. The authors wondered if treatment effects would have been superior with better adherence. Williams ea (2009) conducted a meta-analysis of long-term antidepressant drug therapy and found relapse rates of 23% and 51% for active drug and placebo respectively, and time on treatment significantly influenced the relapse rate.

Agomelatine (Valdoxan) acts at melatonergic receptors (agonist) and 5-HT_{2C} receptors (antagonist). This antidepressant seems to have a sleep restorative effect without suppressing REM sleep.

¹⁴¹⁸ NNT to prevent 1 case of depressive disorder was 22.

¹⁴¹⁹ If prescribing an SSRI concurrently with a TCA lower doses of the latter should be used since SSRIs raise TCA plasma levels.

¹⁴²⁰ Fava ea (2007) suggest that 'recovery' from major depression should include psychological well-being.

Gynaecologists may have been more inclined to opt for oestrogen as a first line treatment of depression in women that would psychiatrists. (Studd, 1992) Nevertheless, transdermal 17-beta oestradiol may improve mood in perimenopausal women.

The neurotic-endogenous and other aetiological distinctions or the presence of life stresses or 'understandability' of depression are no longer regarded as important in defining the presence of disorder and the need for antidepressant drug treatment. Psychotic depression requires the addition of a neuroleptic (e.g. olanzapine plus sertraline: Meyers ea, 2009), the response to antidepressant drugs being poor. ECT may be required. There have been reports of psychotic depressives responding to SSRI on their own, but with high drop out rates due to side effects.

Phases of depression and usage of antidepressant drugs

<i>Acute</i>	Build up to therapeutic dose (TD) from starting dose (lower starting dose in elderly)
<i>Continuation</i>	At least 6 months; use TD to avoid return of symptoms (relapse)
<i>Prophylactic*</i>	Debatable duration (? two years before slow monitored taper; longer if recurrent)

*Suggested indications for maintaining people on longterm antidepressants include highly recurrent depressive disorder (yearly for years; illness cycle < every 3 years; many episodes within 5 year period), severe and incapacitating episodes, protracted episodes, chronic major depression¹⁴²¹, double depression, and residual dysthymia. It is the author's experience that many patients require indefinite treatment.

Even mild atypical cases of depression may respond to medication, classically MAOIs like phenelzine. Pure dysthymia and 'double depression' (dysthymia plus major depression) have been demonstrated to show a complete or partial response to desipramine. Dysthymia may respond to 40 mgs of fluoxetine a day should 20 mgs fail. Dysthymia is not thought to respond to ECT. (Weiner ea, 2001)

Augmentation strategies¹⁴²² may be employed in cases of resistant depression (Cf. below), e.g. lithium added to an SSRI or TCA (this strategy has been said to require an adequate serum lithium level, although as low as 0.3 mmol/L (mEq/L) has been shown to work, and a long trial before declaring it to be ineffective). (Dinan, 1993) However, Birkenhäger ea (2004) found that lithium added to imipramine¹⁴²³ was superior to lithium added to fluvoxamine for treatment of severely depressed inpatients. There is evidence from a small trial (Dinan & Barry, 1989) that TCA-resistant patients respond equally well with either ECT or a TCA-lithium combination. Folkerts ea, (1997) in a study of depressed patients who failed to respond to pharmacotherapy, found ECT to be much more efficacious in the short term than paroxetine. Some patients who fail to respond to a course of ECT (especially unilateral) may respond to a similar course after a gap of, say, some weeks. The occasional patient seems to get more depressed early during a course of ECT only to improve thereafter. Adding an atypical antipsychotic to an antidepressant in major depression may be effective but at the risk of discontinuation due to adverse effects. (Nelson & Papakostas, 2009)

The literature on driving and being on antidepressants is full of so many interacting variables that it is safest to err on the side of safety when counselling patients. (Edwards, 1995a) Whilst it is probably true that depression has a more profound effect on driving than antidepressants, that does not automatically render the latter without potential hazard.¹⁴²⁴

Lithium is not as useful as antidepressant drugs for the prophylaxis of UP depression, and the combination of the two does not seem to confer any benefit. Lithium may have some effectiveness in the treatment of acute depression, but is not comparable to treatment with antidepressants.

Various recommendations have been made as to which antidepressant is safest in epilepsy, e.g. the TCAs trimipramine, protryptiline and doxepin¹⁴²⁵. SSRIs are considered less epileptogenic than TCAs.

¹⁴²¹ Chronic MDD in DSM-IV-TR = full MDD lasting for at least 2 years.

¹⁴²² The decision to augment rather switch an antidepressant may be influenced by a partial (as distinct from no) response to the first drug.

¹⁴²³ Imipramine (Tofranil), withdrawn 2006.

¹⁴²⁴ The Irish reader is referred to the Road Traffic (Licensing of Drivers) Regulations, 1999 (Department of the Environment and Local Government, 1999) for further information.

¹⁴²⁵ Latter not available after November 2006.

Clomipramine, bupropion (especially if dose > 450 mgs/day), and maprotiline (if dose > 200 mgs/day) are particularly likely to induce seizures. MAOIs should be avoided where possible in asthmatics. If they are used, then only steroid-based inhalers should be employed.

Alternatives to lithium in bipolar disorder have been reviewed.(O'Shea, 1993; Vieta ea, 2008a¹⁴²⁶) Initial reports that successful lithium prophylaxis could not be reintroduced with the same success after it had been interrupted may have been unduly pessimistic. Most prophylactic therapies are better at preventing manic than depressive episodes. Lithium prophylaxis may be more successful if there is a family history of response to this drug¹⁴²⁷.(Grof ea, 2002) Although subject to individual circumstances, the author recommends prophylaxis with lithium for patients with a history of one manic attack or one episode of hypomania and one of depression. The usual recommended prophylactic lithium levels range from 0.8-1.0 mmol/L, which may reduce relapse rates but increase side effects over lower levels (0.4-0.8); a balance has to be struck in individual cases. The more rapidly is lithium discontinued the shorter the time is to relapse. Continuation of mild mood swings whilst taking lithium may be a strong indication of relapse on cessation of the drug. Carbamazepine (therapeutic range: 4-12 µg/ml) induces its own metabolism after a few weeks of therapy (autoinduction) so the dose may need to be increased, a problem not found with sodium valproate (therapeutic range of valproic acid: 50-100 µg/ml; according to Allen ea,[2006] levels above 94 µg/ml may give the best response in acute mania). The latter may cause much nausea and vomiting. If carbamazepine has to be combined with lithium, then the dose of lithium may need to be reduced. Some bipolars seem to relapse less often when taking a depot neuroleptic.(Mannion ea, 1999) Lithium plus divalproex sodium resulted in a lower risk of relapse in a pilot study of bipolar I patients (Solomon ea, 1997) when compared with monotherapy. Bipolar I patients stabilised on quetiapine plus lithium or divalproex took longer to relapse than did those on placebo plus lithium or divalproex.(Suppes ea, 2009) A randomised open-label trial (BALANCE Investigators and Collaborators, 2010) found that, for patients with BP-I disorder (irrespective of baseline severity) who require longterm treatment, lithium plus valproate and lithium on its own were more likely to prevent relapse than was monotherapy with valproate.¹⁴²⁸ Lamotrigine (Lamictal), a sodium channel blocker, may have modest antidepressant utility in bipolar depressive episodes¹⁴²⁹ (Geddes ea, 2009) and act as a prophylactic for depressive episodes in BP disorder.(Keck, 2004) Lamotrigine may be associated with a severe skin rash, dizziness, tremor, somnolence, headache, and nausea. However, in one study of BP I patients the only side effect more often seen in the lamotrigine group over placebo was headache.¹⁴³⁰ Obese BP I patients¹⁴³¹ may lose weight on lamotrigine and gain it on lithium.(Bowden ea, 2006)

Treatment of depression in bipolar patients ('bipolar depression') is a common clinical scenario which is still being debated. If the patient is not on prophylactic treatment and the depression is mild, one may try lithium (or an anticonvulsant) or interpersonal or cognitive therapy; if it is severe, one may combine lithium with an antidepressant or increase the dose of lithium (Nemeroff ea, 2001). In general, mood stabilisers may be moderately effective for acute bipolar depression but the available research is somewhat compromised by brevity and high dropout rates.(Van Lieshout &MacQueen, 2010) Breakthrough depression during prophylaxis may respond to optimising prophylaxis¹⁴³² or, if severe, adding an SSRI. MAOIs may be more efficacious than TCAs.(Himmelhoch ea, 1991) A combination of olanzapine and fluoxetine (Symbax) is available for bipolar depression in the US. Refractory cases may require ECT.(Müller-Oerlinghausen ea, 2002) According to Farrelly (2008) treatments with an NNT of < 10 are olanzapine-fluoxetine, lithium-SSRI, quetiapine 300 and 400 mg, and lamotrigine.

Studies of treatment in acute mania often excluded persons incapable of giving informed consent; exclusion criteria do not reflect clinical reality; high dropout rates are common; response is usually defined as at least

¹⁴²⁶ Vieta ea (2008) suggest that the hopes associated with new anticonvulsants, apart from lamotrigine, have not been fulfilled in either bipolar disorder or epilepsy.

¹⁴²⁷ A family history of bipolar disorder, mania followed by depression, and good compliance are associated with good response to lithium; poor compliance, substance misuse, paranoid tendencies, and rapid cycling are associated with a relatively poor response.

¹⁴²⁸ Benefit for the first 2 approaches was demonstrated for up to 2 years. The study was not able to pronounce of the difference in efficacy between lithium monotherapy and lithium plus valproate.

¹⁴²⁹ The advantage over placebo may be larger in more severely depressed patients.(Geddes ea, 2009)

¹⁴³⁰ Lamotrigine may interfere with the efficacy of the contraceptive pill and there may be an increased risk of oral clefts in offspring when it is employed during pregnancy.

¹⁴³¹ A Brazilian study (de Almeida ea, 2009) found an excess of obesity (35.7%) in BP patients compared to the general population.

¹⁴³² Adjusting dosage, adding another prophylactic agent.

50% drop in manic symptom ratings (placebo response being 20-40%). Whilst the evidence is that combined second-generation antipsychotic agents and mood stabilisers represent the most efficacious treatment for acute mania, (Scherk ea, 2007) more research evidence is needed on when and if to taper drugs used in combination, e.g. valproate plus an antipsychotic drug. (Keck, 2003) ECT, lithium and anticonvulsants have all proven efficacies in mania. Higher plasma levels of lithium are used for acute treatment than for prophylaxis, e.g. 1.0-1.5 mmol/L in supervised in-patients for treatment of mania and 0.5-0.8 for the prevention. Low-grade hypomania in-patients who can be supervised outside hospital can sometimes be treated with lithium alone if follow up is frequent enough. Lithium has the advantage of being less likely than neuroleptics of causing a switch into depression, but the disadvantage of a delayed effect. Antidepressants may cause a manic swing. Bupropion may be less likely to induce a switch to mania. Withdrawal of antidepressant drugs may abort a manic episode if done early enough.

Antipsychotics are used more often than lithium for acute mania because they bring the patient's behaviour more quickly under control. A combination of chlorpromazine and a barbiturate was the 'cocktail' of choice in the past. This was replaced in turn by haloperidol, which has been challenged in turn by atypical antipsychotic drugs (risperidone, olanzapine, quetiapine, aripiprazole¹⁴³³, and clozapine) with or without a benzodiazepine. (Green ea, 2000; Khanna ea, 2005; Vieta ea, 2005) Antipsychotic drugs may have specific anti-manic effects that are independent of sedation or an anti-psychotic effect. (Cookson, 2008) In addition, some typical agents may be associated with depression following mania¹⁴³⁴, an effect less likely when atypical are employed. Clozapine may bring mania under control when other approaches fail or are associated with excessive side effects. Olanzapine was superior to divalproex in one study of the treatment of mania, (Tohen ea, 2002) but with a different side effect profile: weight gain, dry mouth, increased appetite, and somnolence versus nausea respectively. Olanzapine was reported as being superior to divalproex in the treatment of acute mania but to be no better than divalproex in terms of rates of relapse of bipolar disorder. (Tohen ea, 2003) However, Tohen ea (2005) found it better than lithium in preventing manic and mixed episode relapse/recurrence over 12 months in bipolar patients acutely stabilised with both olanzapine and lithium, whereas both drugs were comparable in preventing depressive relapse/recurrence. The combination of olanzapine and carbamazepine was not better than carbamazepine alone for mania in another study¹⁴³⁵. (Tohen ea, 2008) A review of RCTs of the comparative safety and efficacy of carbamazepine and lithium in acute mania and as maintenance therapies for bipolar disorder suggested that both drugs may be equivalent. (Coron-Litvoc ea, 2008) According to Yatham ea (2004) quetiapine combined with lithium or divalproex is more effective over 3-6 weeks for mania than lithium or divalproex given alone. Also, Calabrese ea (2005b) found that quetiapine monotherapy was effective in treating bipolar depression. Because of effectiveness and cost issues, Wassef ea (2005) recommend starting with generic valproic acid and only switching to delayed-release divalproex if intolerance occurs. The literature on oxcarbazepine suggests that it might be more efficacious for mild to moderate mania at best. (Grunze, 2008) A combination of ECT and medication might work better than the drug given alone because of putative blood-barrier changes with ECT leading to greater central penetration by the drug. (O'Shea ea, 1983; Skidar ea, 1994) Bilateral ECT given three times weekly for mania has been found to be superior to lithium for the treatment of mania. There is at least one report that unilateral and bilateral ECT had equal efficacy in mania. ECT should mainly be considered where mania does not respond to medication or when the risks attached to drug therapy are unacceptable. (Maixner & Taylor, 2008, p. 60) ECT thrice weekly seems to work faster to relieve depression whereas given twice weekly it has less effect on cognition. The latter frequency is often employed with elders.

Tobacco smoking is probably associated with worse treatment outcomes in mania. (Berk ea, 2008) In general, the combination of BP and substance use disorder is very difficult to treat. (Levy & Weiss, 2009) Scarná ea (2003) describe the use of a palatable drink containing only three branched-chain amino acids (leucine, isoleucine, and valine). These amino acids compete for brain entry with phenylalanine and

¹⁴³³ Aripiprazole may be added to other drugs, such as lithium or valproate, in the management of mania to improve response. (Vieta ea, 2008b) It may also be used solo. (Young ea, 2009) Aripiprazole may also prove useful for residual anxiety in patients treated for depression with an SSRI. (Adson ea, 2005) Aripiprazole is relatively less likely to leave patients feeling 'drugged'. Akathisia and tremor should be sought out and managed appropriately. Hyperprolactinaemia and sexual dysfunction are unlikely. A benzodiazepine may be added whilst sedation is necessary. (Fagiolini, 2008)

¹⁴³⁴ At least some such depressions may be due to extrapyramidal side effects (*akinetic depression*).

¹⁴³⁵ Combination therapy was associated with weight gain and hypertriglyceridaemia.

tyrosine and seem to attenuate central dopamine neurotransmission. In their study,(Scarná ea, 2003) relative to placebo, administration of this mixture to manics lowered Beigel mania ratings acutely over the first six hours. Further work is needed on its longterm effects. An Iranian study (Behzadi ea, 2009) of acute mania in BP I patients (using the Young Mania Scale) found that adding folic acid to sodium valproate was effective in reducing manic symptoms.

The human body normally contains about 0.1% of the therapeutic level of lithium. The peak level determines side effects. Therapeutic effects are related to the 12-hour (since last dose) level. The author tries to test lithium patients' serum lithium level (12 hours post-dose) every 3 months and renal (serum creatinine) and thyroid function (TSH) twice yearly. A pre-lithium ECG is prudent. A recent myocardial infarction (MI) is a relative contraindication to lithium use because of the possibility of an arrhythmia. Patients on anticonvulsants should have their serum levels checked; it is also prudent to check the white cell count and liver function from time to time.

Depression often remits when a patient remains abstinent from alcohol. Less lipophilic beta-blockers such as atenolol or nadolol or the use of ACE inhibitors may help to avoid iatrogenic depression.

In the elderly, it will be recalled that TCAs carry problematic side effects, e.g. urinary retention and postural hypotension. Blurring of vision may be catastrophic for an elder whose sole outlet is reading. Nortriptyline has a role in severe depression. SSRIs are generally more acceptable, but sexual side effects can be a problem 'even' in old age. ECT can be used for a rapid response or where the patient is psychotic.

Rapid cycling

Rapid cycling was more likely to occur in a 13.7 year follow up study (Coryell ea, 2003) if the bipolar disorder (BP) had an early onset (< 17 years old). Reducing TCA intake did not help. Depressive morbidity (esp. if lithium was used without an added TCA), shifts into mania/hypomania, and serious attempts at suicide were common. Alcohol and substance abuse, including cannabis,(Strakowski ea, 2007¹⁴³⁶) may contribute to the phenomenon of rapid cycling and need to be addressed.(APA, 2002, p. 557) The presence of PTSD worsens outcome of BP (Quarantini ea, 2009): patients are less likely to recover, there is an increased proportion of rapid cycling episodes, an increased risk of attempted suicide, and reduced quality of life.

Rapid cycling should be managed by avoiding or stopping antidepressant drugs, by optimising mood stabiliser treatment (starting/adding – Calabrese ea [2005a] found no difference between lithium and divalproex sodium in the treatment of rapid cycling), or, when necessary, adding levothyroxine.(Müller-Oerlinghausen ea, 2002) ECT is reported to induce, be ineffective for, and to abort rapid cycling.(Kho, 2002) Vagal nerve stimulation (VNS) might have some efficacy¹⁴³⁷.(Marangell ea, 2008) Prevention may require early intervention and restricted prescribing of antidepressants.(Schneck ea, 2008)

Resistant (refractory) depression

Assuming the diagnosis to be correct, nonresponse to antidepressant drugs may be due to non-compliance, treatment intolerance, or true treatment resistance. Interestingly, sleep deprivation does not improve anxiety disorders.(Labbate ea, 1998)

Preskorn and Burke (1992) suggest commencing treatment of depression with a TCA or an SSRI. If an adequate trial (full dosage and adequate duration¹⁴³⁸) fails (inadequate response or excess side effects) they would switch from a TCA to an SSRI or vice versa. Should there have been a partial response with the initial agent they would either switch to an alternative drug or attempt augmentation. Should this fail they would try a 'second-line' agent such as the aminoketone bupropion or they would use ECT.(Rush ea, 2006; Trivedi ea, 2006) Rush ea (2008) looked for factors associated with remission with or intolerance to a variety of second-step medications in patients who had an unsatisfactory outcome with citalopram: remission was more likely in the socially stable, non-suicidal patient who who had shown citalopram intolerance and perhaps some response to that drug but it was less likely in people with concurrent anxiety disorders, severe or melancholic depression, or substance misuse, and intolerance for citalopram predicted intolerance for sertraline. Combined MAOI and TCA treatment should be left to specialists. A combination

¹⁴³⁶ Strakowski ea (2000) found that BP patients used alcohol when depressed and cocaine and cannabis when manic.

¹⁴³⁷ Marangell ea (2008) gave open-label VNS for 40 weeks to 9 DSM-IV-TR outpatients with treatment-resistant rapid-cycling bipolar disorder patients and noted a mean improvement of 38.1% over the 12-month study period. Common problems were voice alteration (during stimulation) and hoarseness.

¹⁴³⁸ Ruhé ea (2006) conducted a systematic review of major depression with insufficient response to standard doses of SSRIs and found an increase in dose before 4 weeks to be ineffective and later increases to be of equivocal value.

of a monoamine reuptake inhibitor (MARI) and an MAOI may cause hypotension or the serotonin syndrome¹⁴³⁹. Clomipramine should never be combined with an SSRI or MAOI¹⁴⁴⁰. A TCA can be combined with thyroid hormone, e.g. 25 µg of T3. Potentially, T3 may exacerbate anxiety, cause weight loss, and induce cardiac arrhythmias. T3 appears to be more effective than T4 as an augmenting agent in unipolar depression.(Joffe & Singer, 1990) T3 may be more effective in women than in men.(Coryell & Geddes, 2008, p. 487) Intrathecal TSH has improved some cases of resistant depression. After an initial 2-week drug-free period, a single IV dose of ketamine (NMDA antagonist) led to an antidepressant effect within 2 hours in treatment-resistant major depression.(Zarate ea, 2006) Lithium and an SSRI or TCA is another possibility. Olanzapine added to an SSRI may speed up response rather than improve the longer term effectiveness of an SSRI on its own.(Coryell & Geddes, 2008, p. 487) Venlafaxine has been claimed to produce good results in some refractory depressions as has a combination of mirtazepine and an SSRI.¹⁴⁴¹ Indeed, Blier ea (2010) reported doubling of response rates over fluoxetine monotherapy when the latter was combined with mirtazapine and with mirtazapine-venlafaxine or mirtazapine-bupropion combinations, all combinations being well tolerated. All medications were given from the start of treatment in this study. Testosterone gel has been shown in a preliminary study to alleviate refractory depression in men with low testosterone levels when added to an existing antidepressant regimen.(Pope ea, 2003; see also Shores ea, 2004) Amphetamines are used in the USA in some cases. Modafinil (Provigil) may be efficacious as adjunctive therapy in bipolar depression.(Menza ea, 2000; Frye ea, 2007) ECT should not be seen as a treatment of last resort, an attitude that may lead to excessive delay in its use. Sometimes a second course of ECT works where the first did not, possibly because the illness has moved to a different stage. If an antidepressant does not work before ECT it is unlikely to offer prophylaxis after ECT – consider a different antidepressant or augmentation. Pharmacological treatments need to be continued concomitantly with ECT.(Kennedy & McDonough, 2003) Pindolol¹⁴⁴² is a beta-blocker with 5-HT_{1A} (autoreceptor) blocking properties. Blocking 5-HT_{1A} autoreceptors on cell bodies frees these cells from feedback control and increases serotonin release from nerve terminals. However, beta-blockade could also be the main mechanism whereby pindolol augments SSRIs.(Svensson & Mathé, 2002) It has been used in combination with SSRIs with some useful effect on depression but may promote irritability. Adrenal steroid suppression with metyrapone¹⁴⁴³ may help major depressives already on antidepressants to respond.(Jahn ea, 2004) Metyrapone can cause light-headedness, headache, nausea and fatigue. Alpha-2 blockade using an agent such as idazoxan has also been tried. Many antidepressants, including TCAs and MAOIs, down regulate beta-receptors or the associated NA-sensitive adenylate cyclase. There is a little evidence favouring this approach. Vagal nerve stimulation (VNS) therapy for refractory depression is undergoing early trials. There is evidence from open trials for its efficacy,(Rush ea, 2000; Corcoran ea, 2006) which may increase over time¹⁴⁴⁴, but more knowledge is required about side-effects, e.g. cough and vocal cord palsy from surgery. Most refractory depressions will eventually remit, although it may take a long time to happen.

Physical treatments in physically ill depressives

Doses should be started low and increased slowly. MAOIs are best avoided because of potential drug interactions. TCAs have analgesic effects. Poor renal or hepatic function, low plasma protein concentration, and drug interactions alter antidepressant metabolism. As a general but not absolute rule, avoid ECT in the following situations: recent cerebral bleed, raised intracranial pressure, brain tumour or other large intracranial masses, recent ventricular dysrhythmia, sickle cell disease, large anaesthetic risk, aortic or

¹⁴³⁹ **Serotonin syndrome:** delirium, agitation, restlessness, diarrhoea, hyperthermia, unstable vital signs, ataxia, dysarthria, rigidity, myoclonus, hyperreflexia. Drug causes include agents that increase formation (L-tryptophan), release (Fenfluramine, phentermine, amphetamine, cocaine, L-dopa, LSD, pethidine, mirtazapine), reduce uptake (SSRIs, SNRIs, opioids, and bromocriptine), act as agonists to (buspirone and triptans like sumatriptan), increase the sensitivity of postsynaptic receptors for (lithium), and decrease metabolism of (MAOIs including the antibiotic linezolid) serotonin.(Ahuja & Cole, 2009)

¹⁴⁴⁰ That being said, some experts have used clomipramine plus an SSRI for refractory OCD.

¹⁴⁴¹ Patients should be monitored for the serotonin syndrome.

¹⁴⁴² Evidence for augmentation with pindolol or valproate was described as poor (Joubert, 2007) but doses of pindolol may have been too low in early studies; there is evidence that pindolol may hasten response rather than increase rates of response.(Coryell & Geddes, 2008, p. 487)

¹⁴⁴³ Inhibits P450_{11β} that allows 11β-hydroxylation, the final step in adrenal cortisol production.

¹⁴⁴⁴ Median time to response of 9 months in Schlaepfer ea.(2008)

cerebral aneurysm, and recent CVA. TCAs are best avoided under the following circumstances: recent MI, heart block, congestive cardiac failure (CCF, danger of hypotension), closed angle glaucoma, enlarged prostate, renal failure, epilepsy (see above – do not use maprotiline!), liver failure (lower doses if necessary in mild cases, avoid if severe), cimetidine (raises TCA levels), constipation, agranulocytosis, and porphyria. MAOIs are best avoided in the presence of CCF, hypertension (enhancement of antihypertensives), carbamazepine, CVA, liver failure (use reduced dosage), pheochromocytoma (do not even use moclobemide), and hyperthyroidism (avoid tranlylcypromine and moclobemide). Lithium may cause problems if used in certain scenarios: CCF (excretion reduced by ACE inhibitors and diuretics), hypertension (diuretics reduce excretion and methyl dopa increases chances of neurotoxicity), renal failure (toxicity), Parkinson's disease (CNS toxicity if combined with sumatriptine), severe diarrhoea, Addison's disease, and hypothyroidism. SSRIs may be problematic in epilepsy (levels increased by phenytoin and carbamazepine), GIT disorders (nausea), and fluoxetine plus selegiline¹⁴⁴⁵ in Parkinson's disease may cause a confusional state. Amphetamines are sometimes used in the USA. (Lingam ea, 1988)

Prognosis

'Depression and diabetes are alike in burden, and both have chronic courses marked by periods without symptoms and by occasional emergencies'. (Andrews, 2001)

'The long-term outcome of depression still shows high recurrence rates and does not appear to have changed in the last 20 years.' (Kennedy ea, 2003)

Finding in studies of prognosis may depend on factors such as what is measured (e.g. readmission or relapse), who is studied (e.g. confined to patients with multiple admissions), and the degree of effort made to validate diagnoses. (Kessing ea, 2004) Contrary to earlier opinion, Angst (1992) pointed out that most depression is recurrent, there being a 78%¹⁴⁴⁶ recurrence rate after 10 years in one study. Major depression has a high rate of recurrence, especially in the first months following recovery. According to Angst (1990) one and three episodes of depression carry a 50% and 90% chance of recurrence. Similarly, Delgado and Gelenberg (1996) put the recurrence rate for major depression after one or two episodes at 50% and 80-90% respectively. The risk of recurrence does not differ for depression whether it is related to bereavement or not (Karam, 1994) and the validity of the bereavement exclusion for the diagnosis of major depression in DSM-IV has been questioned because of the similarity between depression caused either by bereavement or other stresses. (Kendler ea, 2008b) A multi-centre prospective (6 years) follow-up in Japan of an inception cohort (N = 95) of previously untreated unipolar major depressives found that less than half the patients remained virtually without symptoms for 2 or more years post-recovery, and that residual symptoms at recovery predicted earlier recurrence. (Kanai ea, 2003; see also Nierenberg ea, 2010) A Cambridge (UK) follow-up of mainly severe recurrent depressives found that 92% recovered during follow-up, two-thirds then suffering a recurrence, 17% suffered from an episode of depression of at least 2 years duration, and the more severe the illness the poorer was the outcome. (Kennedy ea, 2003) An American 20-year follow-up of major depression (Coryell ea, 2009b) found that persistence of symptoms does not change as patients age and that earlier age at onset seemed to predict greater morbidity. Prophylactic medication reduces the risk of recurrence by more than half. There seems to be a trend toward increasing severity with subsequent episodes that may not be affected by prophylactic measures. All antidepressants are probably effective prophylactics, although not all have been rigorously tested for this property. Do antidepressants lose their efficacy over time? According to Demyttenaer, (1999) this can affect up to one in three patients. Should they do so we must consider non-compliance, loss of placebo effect, pharmacological tolerance, increased disease severity, change in disease pathogenesis, accumulation of a detrimental metabolite, unrecognised rapid cycling, and prophylactic inefficiency. In a NIMH follow up of major depression over 5 years, 20% failed to recover from the index episode, developing a chronic course instead. (Keller ea, 1992) Anxiety in depressed people is associated with a poorer response to antidepressant treatment. (Fava ea, 2008) However, in a population survey, Mykletun ea (2009) found a mortality hazard ratio of 1.52 for case-level depression (for smoking it is 1.59) but co-morbid anxiety lowered the mortality risk.

East Baltimore prospective study of major depression (MD) (Eaton ea, 2008)

¹⁴⁴⁵ Selegiline is a selective, irreversible MAO-B inhibitor. Dietary precautions are required for higher (9 or more mg) but not lower (6 mg) doses of selegiline.

¹⁴⁴⁶ Figures vary.

23-year follow-up (13 years minimum), population-based
 3481 household residents in 1981, including 92 first episode MD
 Greater likelihood of onset of MD, longer episodes, and (slight) increase in recurrences in females
 Sex did not predict recovery
 Median episode length = 12 weeks
 15% of the 92 had no year without a recurrence

Married women with major depression may have a particularly good outlook if they rate the marital relationship as good. A long delay before receiving treatment for major depression and high premorbid neuroticism predicted symptom persistence in a study by Scott *et al.* (1992) Initial diagnosis of personality disorder in unipolar depression augurs poorly for very long term psychiatric and social outcome. (Newton-Howes *et al.*, 2006) It also delays recovery in major depression (Gorwood *et al.*, 2010) and may reduce the efficacy of interpersonal psychotherapy. (Joyce *et al.*, 2007).

Psychotic depression is associated with a lifetime illness of greater severity than non-psychotic major depression. Also, not all of their episodes are necessarily psychotic. Mood-incongruent psychotic features in mania and depression predict a poorer outlook¹⁴⁴⁷, as do residual symptoms after treatment of major depression. There may be genetic overlap of bipolar affective disorder with schizophrenia. (Goes *et al.*, 2007) Some authors regard the prognosis for depression in the elderly as being good if only it were treated aggressively enough, while others view it as being relatively poor. According to Chew-Graham *et al.* (2004) it has not changed since Millard's (1983) article, i.e. a third improve, a third remain unchanged, and a third disimprove. There is even some evidence for a better prognosis relative to younger depressives. Early onset, recurrence, and poor premorbid personality functioning have been described as poor prognostic factors in the depressed aged. Whatever treatment works, it should be maintained to prevent relapse: Chew-Graham *et al.* (2004) suggest that we adopt a chronic disease model for the elderly depressed. The results of some studies of prognosis in the depressed elderly are summarised in the table.

Prognosis in the elderly depressed

Year	Results	Comments
1993	47% improved at 15 months 71 % better at 4 years	Treatment (drugs and ECT) resistant cases
1993	Less likely to be recovered at one year if spouse or adult child had psychiatric symptoms (especially depression, anxiety, somatisation), if carer finds role difficult or is in poor physical health	Elderly admissions, RDC major depression
1997	Cognitive impairment = poor prognosis	Chronically hospitalised patients
1997	60% of elderly hospitalised patients remained well or had treatable relapses/recurrences; 15-20% of developed chronic symptoms; worse prognosis in community (? low rates of treatment)	Meta-analysis
1997	Persistent anxiety in remitted depression is associated with earlier relapse	
2002	Cognitive decline more common if depressed, <i>espc.</i> if persistent rather than episodic	Large sample from Nantes; cognitive decline = drop of at least 3 points on MMSE* at 4-year follow-up
2005	Review of 24 publications	Episodes remit but relapse rate higher than in middle life because of medical co-morbidity and recurrent depression from earlier life
2006	85 or older in Leiden – depression is common and persistent	No formal diagnosis of depression; low MMSE score led to exclusion (< 19)

*MMSE, Mini-Mental State Examination

Up to 60% of BP cases are unable to return to premorbid levels of social and vocational functioning. (MacQueen *et al.*, 2001) Severe anxiety during BP mood episodes seems to mark an illness of significantly greater long-term depressive morbidity. (Coryell *et al.*, 2009c) Over 80% of patients who have a

¹⁴⁴⁷ But do not obviate the diagnosis.

manic episode will have one or more recurrences. Patients who switch from one pole of BP disorder to another without an intervening normothymic interval may have a poorer prognosis than those who experience euthymia between episodes. (Maj et al, 2002) An outcome study of children with a prepubertal or early adolescent-onset BP disorder found that 65% recovered after a mean of 36 weeks of treatment, and 55% relapsed at an average of 38.6 weeks following recovery. (Geller et al, 2002) In adults with a diagnosis of childhood BP I disorder the 44.4% frequency of manic episodes reported by Geller et al (2008) supports continuity between child and adult BP I disorder. Geller et al (2008) also found similar rates of substance use disorder in people who developed BP I in either childhood or adulthood.

Common reasons for recurrences in bipolar cases are inadequate management (e.g. too low a lithium serum level) and non-compliance. Reasons for non-compliance in patients with affective disorders include side-effects¹⁴⁴⁸ like memory problems, weight gain, co-ordination difficulties, tremor, polydipsia; a wish to avoid stigma; symbolism between prophylactic regimen and having a chronic illness; attribution of all sorrow to the world or the self; reduced creativity¹⁴⁴⁹; not wanting treatment when feeling well; medication being seen as a sign of moral cowardice or weakness; lack of insight¹⁴⁵⁰; advice from third parties; and storing tablets for an intended overdose. Pseudo-compliance is not rare, e.g. the patient who takes their lithium for a few days before each phlebotomy. Non-compliance with lithium, the commonest reason for relapse in bipolars, has been estimated to affect 18-53% of cases. The patient should have his medication and the reasons for it explained. Written information is helpful, as are simple regimens. The patient should be encouraged to state frankly if the medication is later abandoned.

Affective disorder patients may be at particular risk of developing tardive dyskinesia.

The average failure rate for lithium prophylaxis is 33%, failure being defined as an episode needing admission or the addition of further drug treatments. Only one-fifth of patients who are suitable for lithium can expect to have no recurrences.

Depression in general practice¹⁴⁵¹ (GP)

GPs, at least in the UK, appear to increasingly use symptoms rather than diagnostic labels to categorise illnesses such as depression. (Rait et al, 2009) GPs see more (typical, younger and milder) cases of depression than psychiatrists, they initially miss the diagnosis relatively more often than psychiatrists (but may pick it up eventually: Kessler et al, 2002; Mitchell et al, 2009), they may diagnose depression when it is not there (Mitchell et al, 2009), they may be relatively reluctant to search for depression in the elderly, (Chew-Graham et al, 2004) and they are less likely to give adequate doses of antidepressant drugs (apart from SSRIs and perhaps lofepramine) than are psychiatrists. (e.g. Blacker & Clare, 1988; Maddox et al, 1994) However, even psychiatrists are not immune from inadequate dosing. (Macpherson & Robson, 1994) According to one meta-analysis, GPs might improve their diagnostic yield if they re-assessed cases over a longer time period rather than relying on a once-off examination. (Mitchell, 2009) GPs also see more mixed pictures of anxiety-depression. Also, one meta-analysis suggested that low doses TCAs (75-100 mgs/day) are superior to placebo and that higher doses confer no improvement in efficacy but do increase the dropout rate from side effects. (Furukana et al, 2002) MacGillivray et al, (2003) in their systematic review and meta-analysis, found that antidepressant efficacy studies in GP had significant methodological shortcomings. However, a Cochrane systematic review (Arroll et al, 2009) suggests that TCAs and SSRIs are effective treatments for depression in primary care settings. GPs should consider referral to a psychiatric colleague if the diagnosis is uncertain, to have questions concerning management clarified, if treatment efforts fail, if specialist supervision of treatment is required or if non-drug therapies are being considered (assuming the resources are in place). (see HSE & ICGP, 2006) Further reasons include those situations where in-patient investigation is needed, the disorder is severe, the patient is violent (with adequate forewarning by the GP) or suicidal, there is self-neglect, or the patient is psychotic. Depression associated with another problem, such as alcohol abuse schizophrenia or an eating disorder should also be considered for referral. Referral is

¹⁴⁴⁸ Adverse effects are only one factor in non-compliance. Greater compliance with SSRIs relative to TCAs has not been a universal finding. (Lader, 2007)

¹⁴⁴⁹ The relationship between mental illness and genius is controversial. (Keynes, 1995; Schildkraut & Otero, 1996; Andreasen, 2001, pp. 200-1; Pandarakalam, 2005) Whilst a Swedish prospective study (MacCabe et al, 2010) found an almost fourfold increased risk among adolescents doing well at school for later bipolar disorder it also found a modest association between those with the lowest school grades and later bipolar disorder.

¹⁴⁵⁰ E.g. psychotic depression or severe mania.

¹⁴⁵¹ King et al (2008) suggest that depression and anxiety disorders may be more common in GP in some European countries (UK and Spain) than in others (Slovenia, The Netherlands).

also indicated where the relatives want it, where the GP's advice is not accepted or believed, or when the GP needs support because of, for example, an angry patient or family. Simply asking if the patient (a) often felt bothered by feeling down/depressed/hopeless or (b) often been bothered by little interest or pleasure in doing things (both [a] and [b] during the past month) could detect most cases of depression in GP in one study. (Arroll ea, 2003)

Thompson ea (2000), in the Hampshire Depression Project, found that educating UK GPs in depression detection and treatment (using clinical practice guidelines) failed to improve recognition or outcome. An observational study of risk factors for depression in GP (Bottomley ea, 2010) suggests that it may be more productive to try and tackle proximal than distal risk factors because the latter may be more entrenched.

Carer stress

Stress among carers looking after BP disorder patients arises from the patient's symptoms and role dysfunction. It also comes from the effects of the disorder on the carer's occupation and leisure time. Perceived stress may be greater if the relative feels that the patient should be able to control his illness or symptoms or if the relative feels helpless in controlling these phenomena. A full understanding of the seriousness and prognosis of the disorder may also increase stress. (Perlick ea, 1999) Depression in carers may develop follow erosion of coping powers secondary to perceived stigma. (Perlick ea, 2007)

Suicide and Parasuicide¹⁴⁵²

Attempted suicide (AS)

The term AS is associated with Stengel. Alternative terms are parasuicide (Kreitman), deliberate¹⁴⁵³ self-harm (Morgan) and act of self-harm (Bateman, who avoids implying intent or motive). AS is about ten times more common than completed suicide¹⁴⁵⁴. Factors reported to increase the likelihood of AS are shown in the table. In the real world, any psychiatric disorder may be accompanied by suicidal behaviour or self-harm. The complex role of unemployment has been discussed by O'Shea. (2000c; see also Gavin ea, 2010) Rates of parasuicide rose in most Western countries in the 1960s. Pathways to CS may differ significantly for different ethnic groups living in the same country. (Clarke ea, 2008) People who present to hospital emergency departments with a specific and spontaneous complaint of suicidal ideation with no accompanying act of self harm are more likely to have a personality disorder or to be alcohol dependent than to have a depressive illness according to Hawley ea. (1991) Indeed, individuals presenting *with* self-harm often have histories of dependent, harmful or hazardous drinking that may easily be missed unless careful inquiry is made, including the use of an alcohol screening instrument such as *AUDIT*. (Holdsworth ea, 2010) 6.5% of over 75,000 people (aged 16-64 years) discharged from psychiatric inpatient care in England were admitted at least once in the following year (Gunnell ea, 2008); risk of self harm was associated with recent admission for self harm, female sex, being young, depression, personality disorder, substance abuse, and brief admission. Most cases of AS probably do not present to hospital. (Hawton ea, 2002)

Canadian survey: people aged 15 years and older (Robertson Blackmore ea, 2008)

0.6% endorsed a 12-month suicidal act

Risk factors - female sex, separated or divorced marital status, being unemployed, having a chronic physical health condition, and experiencing major depression during the same 12 months as the act

Scottish survey: 15-16 year old pupils (O'Connor ea, 2009)

13.8% reported self-harm (girls: boys = 3.4:1) and 71% of these self-harmed in past year

Risk factors in both genders – smoking¹⁴⁵⁵, bullying, sexual orientation concerns, self-harm by family, and anxiety

¹⁴⁵² See O'Shea ea (2000) and Hawton and van Heeringen (2009) for reviews. Walsh (2008) reminds us that suicides once had their remains hung from the Five Lamps in Ballybough, Dublin!

¹⁴⁵³ 'Deliberate' is often dropped by authors who stress the heterogeneous nature of this group. Also, some patients may perceive it as pejorative.

¹⁴⁵⁴ Non-fatal suicidal behaviours in adolescence and young adulthood may be more common than suggested by cross-sectional studies or parental reports. (Brezo ea, 2007)

¹⁴⁵⁵ Boden ea (2010) suggest that cigarette smoking may even cause depression.

Risk factors in girls: drug use, physical abuse, serious boy/girlfriend problems, self-harm by friends, and low levels of optimism

Germany/Midwestern USA: school going adolescents (mean age 14.8 years, range 14-17 years)(Plener et al, 2009)

25.6% endorsed at least one act of non-suicidal self-injury, 9.5% of these having hurt themselves more than 4 times; 6.5% had a history of AS; adolescents in both geographical areas were similar in terms of self-injury and suicidal behaviours

Having a friend who committed suicide increases the likelihood of suicidal ideation in the self.(Hawton et al, 2002) A cross-sectional, 17-country study (Nock et al, 2008) found that 60% of changes from ideation to plan and attempt occurred within a year of having the idea, and consistent risk factors included female sex, relative youth, low education level, single marital status, and having a mental disorder; the strongest nosological risk factors were mood disorders in wealthy countries and impulse control disorders in low/middle income nations. In the opinion of Simon and Savarino (2007) suicide attempts are not caused by antidepressants but reflect referral patterns.

Factors affecting 'attempted suicide' (AS) rates¹⁴⁵⁶

The reader will notice apparently contradictory reports, e.g. relating to Christmas Day. Also, the direction of causation may be difficult to disentangle. *Not everyone agrees that mental disorder is always present and AS is not unique to any psychiatric disorder. Chiles & Strosahl (2005, p. 260) suggest that suicidality is associated with an underlying psychiatric disorder in 50% of cases.*

Of self-harm 'cases' presenting to Irish emergency departments in 2007 17% were repeat visits. 17,000 deliberate self-harm (DSH) presentations (9,218 individuals) were made to Irish A & E departments in 2008; the rate increased from 188 to 200/100,000 from 2007 to 2008, representing rises of 11% and 4% in males and females; and the peak rates for males and females were in the age groups 20-24 and 15-19 years respectively. 11,966 people with DSH presented to Irish hospitals in 2009.

Increasing

Adolescence – *much serious mental illness starts at this age and suicide is the third leading cause of death in 15-19 year old in the USA; 17% of high US school students consider suicide and 8.4% attempt suicide at least once during the past year; parents are often unaware that anything is wrong and only a minority give a warning;(Friedman, 2006) impulsive aggression (highly heritable) may be a common end result of many factors (suicide seen as a solution, poor cognitive flexibility and problem solving abilities, difficulty inhibiting inappropriate responses); suicidal behaviour may be transmitted in families independent of psychiatric disorders (a genetic basis is supported by adoption studies); childhood abuse/neglect may compound genetic vulnerability (Brent & Mann, 2006); and local poverty is associated with suicidal thoughts and attempts.(Dupéré ea, 2009) Emotional unavailability of mother in early life is another predictive factor.(Weich ea, 2009)*

Alcohol/substance abuse/misuse – *smoking tobacco¹⁴⁵⁷; high scores on AUDIT common in psychiatric admissions of both sexes and alcohol misuse strongly associated with suicidality (McCloud ea, 2004); in an Irish context alcohol consumption was evident in 41% of episodes of deliberate self-harm (48% males, 38% females)(IMO Position Paper, 2008, p. 5)*

Anxiety - *Fairweather ea (2006) found that AS differed from suicide ideation, not on the levels of depression and anxiety, but by unemployment, poor physical health, and relationship problems.*

Availability, *e.g. paracetamol¹⁴⁵⁸; co-proxamol¹⁴⁵⁹ (paracetamol + dextropropoxyphene) accounted for 5% of all suicides in England & Wales during 1997-99 – the odds of dying after co-proxamol OD was 2.3 that for TCAs and 28.1 that for paracetamol.(Hawton ea, 2003a)*

Bipolar I disorder – *risk factors for lifetime AS among French patients admitted for mania were multiple admissions, depressive or mixed polarity in first episode, stressful life events before illness onset, younger age at onset, no well intervals, female sex, more prior episodes, and cyclothymic temperament.(Azorin ea,*

¹⁴⁵⁶ From the literature.

¹⁴⁵⁷ Perhaps by causing 5-HT deficiency (Malone ea, 2003) or by background factors and life circumstances common to smoking and suicidal behaviour.(Boden ea, 2008)

¹⁴⁵⁸ **Paracetamol:** A common reason for liver transplantation; the specific antidote, intravenous N-acetyl-cysteine, has to be given within 10-12 hours to achieve maximum effect; if this is not available one can use oral methionine. A toxic breakdown product of paracetamol is scavenged by glutathione; when the body runs out of glutathione (common in alcoholics) the paracetamol metabolite attaches itself to liver cells and kills them. From 2009 in Ireland paracetamol must be supplied by a pharmacist.

¹⁴⁵⁹Withdrawal of co-proxamol in England Wales (2007) appears to have led to less deaths from this agent and no substitution with other analgesics for the purposes of suicide.(Hawton ea, 2009)

2009) Fiedorowicz ea (2009) found that polarity did not predict future suicidal behaviour whereas age, helplessness, and active substance abuse did. In this 25-year prospective NIMH study, 909 participants met criteria for major depression or bipolar disorder. 4,204 mood cycles were recorded.

Bipolar II disorder – in a review and meta-analysis, Novick ea (2010) found that while BP II disorder was associated with significantly increased AS rate there was no significant risk between this an AS rate in BP I disorder

Birth length - short male birth length increases chances of violent suicide attempt as adult¹⁴⁶⁰

Bullied and bullies in Finnish schools had increased suicidal ideation; being bullied in New South Wales correlated with psychosomatic complaints and poor mental health; bullied Irish adolescents was associated with depression and suicidal ideation.(Mills ea, 2004)

Certain dates/times of year, e.g. St Valentine¹⁴⁶¹, Christmas Day; female admissions increased during 2-4 January in Edinburgh. Female admissions in Edinburgh increased during summer (others report spring/early summer excess).

Child neglect or maltreatment/maladaptive parenting¹⁴⁶²

Child sexual abuse – American data suggests a later connection with AS, especially in early adolescence, mediated mostly, but not completely, by psychopathology. Melhem ea (2007) found such abuse to be one factor (with mood disorder, impulsive aggression, parental AS, and self-reported depression) preceding early-onset suicidal behaviour in offspring of mood-disordered parents. Sexual abuse as a child in Quebec, especially if abused by immediate family.(Brezo ea, 2008¹⁴⁶³). The 2000 British National Survey of Psychiatric Morbidity (Bebbington ea, 2009) found that sexual abuse is a significant antecedent of suicidal behaviour, more so for females.

Childhood behaviours contradicting typical gender norms¹⁴⁶⁴ has predicted suicidal ideation by 15 or suicidal acts by 18

City life, e.g. Limerick, and possibly other urban Irish areas.(Corcoran ea, 2003; National Suicide Research Foundation, 2002)

Comorbid psychiatric disease in depressed women in the community (McHolm ea, 2003)

Criminal record

Depression: For one reason or another, those who commit AS fail to tolerate similar levels of depression suffered by those who do not harm themselves deliberately.(Malone ea, 1995) Depression and hopelessness and important ingredients in adolescent self-harm (Webb, 2002) and hopelessness in adolescent AS is often disproportionate to other features of depression.(Mann ea, 1999) DSM-IV major depression risk factors for AS incl. severity of depression, lack of a partner, previous AS, and time spent depressed.(Sokero ea, 2005) Hopelessness and poor social integration in elderly depressives.(Dennis ea, 2005) Severity of depression during current episode.(Vuoriletho ea, 2006) Unipolar depression plus gray matter hyperintensities on MRI may increase likelihood of AS.(Ahearn ea, 2001) AS in bipolar disorder is associated with atypical depression, family history of suicide, depression at index episode, and cluster B personality disorder.(Sánchez-Gistau ea, 2009)

¹⁴⁶⁰ *J Epidemiol Community Health* 2008;62:168-73.

¹⁴⁶¹ February 14.

¹⁴⁶² Perhaps via severe interpersonal problems in adolescence.

¹⁴⁶³ In this study externalising behaviour was also associated with AS.

¹⁴⁶⁴ E.g. aggressive girl, dependent boy.

Dissocial personality disorder/impulsive aggressivity/conduct problems/identity problems (e.g. Brezo ea, 2006)

Early discharge against medical advice¹⁴⁶⁵ and **first year after discharge**

Female sex – However, males 55 years and older showed an increase in AS in Oxford during 1990-2000 and there are other findings to suggest that the disparity between the sexes may be narrowing in Manchester, UK

Hallucinations in first-episode psychosis

Homelessness and housing problems

IQ. Batty ea (2010) looked at how early adulthood IQ influenced subsequent AS in Swedish males with and without psychosis and found that men without psychosis with low IQ scores were at increased risk (although the authors state that their research may have ‘slightly overestimated’ any effect) but there was no evident association among men with psychosis

Low cholesterol. Is cholesterol a CNS marker for serotonin? Also, excess alcohol may increase high-density lipoprotein levels and hence the amount of cholesterol transported peripherally, causing a lowering of the serum cholesterol. Could interleukin-2 be affected? Statins may induce depression. Not all studies find a connection with low cholesterol levels, e.g. Almeida-Montes ea.(2000) Low lipid concentrations have correlated with self-injury and borderline features in patients with dissociative disorder.(Agargun ea, 2004) Dietary cholesterol supplementation reduces aggression in sufferers from Smith-Lemli-Opitz syndrome.(Lalovic ea, 2004) In a study by Garland ea, (2007) low plasma essential fatty acids plus low cholesterol concentrations were associated with self-harm as well as impulsivity and affect, but not related to platelet serotonergic measures. The same group (Hallahan ea, 2007) reported reduced indices of self harm in repeated self-harmers given long-chain omega-3 essential fatty acids.

Low self-esteem

Low socio-economic status (Taylor ea, 2004)

Menstrual cycle (late luteal and follicular phases¹⁴⁶⁶) and **premenstrual syndrome** (Saunders & Hawton, 2006)

Panic disorder¹⁴⁶⁷

Parental concern. Parental concern may be more accurate than clinician risk assessment in predicting repetition of self-harm.(Cassidy ea, 2009)

Past psychiatric treatment.(Vuoriletho ea, 2006)

Personality disorder.(Vuoriletho ea, 2006) Borderline personality disorder, especially if they show aggressiveness.(Keilp ea, 2006)

Prefrontal dysfunction e.g. impaired visuospatial conceptualization, spatial working memory, inhibition, and visual attention.(Raust ea, 2007)

Previous AS (in self or parents or friends)

Relationship problems (e.g. Sinclair & Green, 2005)

Sexual identity problems/gays/lesbians/bisexuals (Warner ea, 2004)

SSRIs (strongly disputed by, e.g. Gibbons ea, 2007b) Emergence of suicidal ideation during citalopram treatment may be associated with genetic markers within genes encoding ionotropic glutamate receptors.(Laje ea, 2007) Predictors of self-harm such as a history of self-harm suicidal ideation, family conflict, and drug/alcohol abuse may be more important than being on SSRIs.(Brent ea, 2009¹⁴⁶⁸)

Teenage mothers (e.g. Ekéus ea, 2006)

¹⁴⁶⁵ AMA – 8% in UK in 1991 increasing to 17% in 1997 in one cohort study.

¹⁴⁶⁶ Low oestrogen levels.

¹⁴⁶⁷ Comorbid depression or alcohol abuse may be more important than panic disorder *per se*.(Vickers & McNally, 2004)

¹⁴⁶⁸ This was a study of depressed adolescents who did not respond to one SSRI. Patients were given another SSRI or venlafaxine, with/without CBT. Episodes of self-harm, when they occurred, occurred in the first few weeks of treatment. These authors found higher risk for venlafaxine (possibly given for ‘deeper depression’) and benzodiazepines (possible disinhibition). This requires further study. It must be remembered that analysis of many variables is likely to ‘throw up’ results that may or may not have clinical implications as distinct from media interest.

Unemployment - Not surprisingly, job insecurity is associated with feeling depressed (Meltzer ea, 2010)

Withdrawal of antidepressants - Discontinuation of SSRI or tricyclic antidepressants was associated with a five-fold increase in suicidal behaviour in unipolar depressives.(Yerevanian ea, 2004)

Possibly decreasing

Antidepressants in adults (Stone ea, 2009)

Antiepileptic drugs in bipolar disorder (Gibbons ea, 2009)

Caribbean origin in UK for psychotic older people, but such protection is absent for psychotic younger persons (McKenzie ea, 2003)

Christmas Day Female admissions in Edinburgh decreased during winter, especially during Christmas Day; self-poisoning less likely on Christmas Day

Early detection/treatment of first episode schizophrenia (Melle ea, 2006)

'Phoning patient a month after discharge from emergency department after deliberate self poisoning.(Vaiva ea, 2006)

School holidays (Hawton ea, 2003b)

Time-limited CBT (Slee ea, 2008)

Neutral

No **monthly/seasonal pattern** for male admissions in Edinburgh

Offering a **crisis support telephone call** did not influence repetition rate

Properly conducted trials in schizophrenia that use placebo (Storosum ea, 2003)

CYP2D6 and CYP2C19 polymorphisms¹⁴⁶⁹ in schizophrenia (Kobylecki ea, 2008)

Psychodynamic and cognitive-behavioural approaches may help in reducing suicide risk. The latter may correct cognitive distortions leading to hopelessness. Establishment of a therapeutic alliance is essential. The therapist should address any underlying fantasies such as the wish to punish oneself or another person, to manipulate, or to put a stop to suffering. Has the patient internalised the capacity to contain psychic stress, does he find solace in keeping suicide as a future possibility should circumstances deteriorate, or does he harbour a wish to die simultaneously with a wish to live? Has he integrated the conflicting (good and bad) parts of his personality? Has he become calm because he is resigned to self-termination or because his depression has lifted or because his girlfriend is returning to him? The therapist must not collude with the patient who is in denial concerning the threat to his life.

Services for self-harm patients are often poorly planned and delivered.(Suominen ea, 2004) These patients are often either seen by trainees in psychiatry or by no psychiatrist at all.(Anonymous, 2010) There is wide variation in terms of disposal and implementation of recommended service structures.(Bennewith ea, 2004) Also, up to 50% of AS cases fail to keep follow-up appointments¹⁴⁷⁰. Follow-up GP appointments for first episode patients may even have adverse effects!(Bennewith ea, 2002) Whilst there is no substitute for an assessment of suicidal risk and the formulation of a care plan,(Edwards, 1995b) one relatively short follow-up of psychosocial intervention found that one needs to intervene in twelve cases to prevent self-poisoning in one person.(Kapur ea, 2002) Also, whilst Hasan and Owens (2003) found that 53% and 26% of 237 patients who later self-poisoned saw their GPs in the previous month and week respectively the patients recounted that their main expectations concerned prescriptions, sick-notes and physical check-ups. Even more interesting, in Ireland only 23% and 8% of CSs during 1997-8 visited their GP and mental health professional respectively within one month of death.(Departments of Public Health, 2001) Emergency department staff may rate more cases as at high risk of repetition than do specialist staff, and high-risk approaches to prediction suffer from the fact that many repeaters are in the lower risk groups.(Kapur ea, 2005)

¹⁴⁶⁹ Such polymorphisms are associated with either drug accumulation or rapid elimination of psychoactive drugs.

¹⁴⁷⁰ In a study of teenage school pupils only 12.6% of those who reported deliberate self-harm in the previous year said that they had been seen at a hospital.(Hawton ea, 2002)

Apart from a past history of AS, repeated AS is associated with past psychiatric history, non-adherence, drug misuse, hopelessness, high suicidal intent, a forensic history, low social status, and being unemployed. Impairment in problem solving is associated with deliberate self-harm. The person attacks him/herself instead of looking at different ways of directly changing the situation, trying to distract him/herself, avoiding or resigning him/herself to difficulties, seeking comfort from others, avoiding being preoccupied with the problem, showing annoyance with those causing the difficulty, or engaging in self-comforting thoughts. Passivity and problem avoidance, with associated lowering of self esteem, may be helped by intensive aimed at improving problem solving ability.(McAuliffe ea, 2006)

Suggestions for a plan to reduce suicidal behaviour (Platt ea, 2005¹⁴⁷¹)

Increase opportunities to:
 Develop life skills
 Achieve educational qualifications
 Get a suitable job
 Undertake meaningful activity
 Participate in community life
 Prevent concentration of vulnerable people in areas with drug/alcohol problems

AS is associated with increased risk of dying from natural causes, accidents, and homicide, not just from suicide.(Hawton ea, 2006)

Completed suicide (CS)

'The patient has a direct relationship with his own death in suicide....the clinician's role and room to influence the outcome is quite often exaggerated'.(Oyebode, 2005)

'There may be controversy about the risk posed by antidepressants, but there is none about the risk associated with untreated depression'.(Friedman & Leon, 2007)

Suicide is the intentional taking of ones own life. It is often ultimately impulsive. Legally, suicide means that a person 'acting alone'¹⁴⁷² did the act that led to death and the act was done in order to cause death, and intent at the time of the act must be shown beyond reasonable doubt. Practising psychiatrists will already have experienced CS by one or more patients or will do so in the future.(Simon, 2008, p. 1639) According to most of the literature, mental illness,(e.g. Agerbo ea, 2002) *or at least great distress*, is the most common accompaniment. Long term follow up shows that psychiatric patients kill themselves much more often than those who do not have such a history.

Risk of CS following AS (Tidemalm ea, 2008)

Aim – relationship between co-existing psychiatric disorder and CS after AS
 Cohort study, 21-31-year follow-up of people (53% female) admitted to hospital for AS 1973-82
 A high proportion of CS took place in the first 12 months
 Highest short-term risk – bipolar and unipolar affective disorder and schizophrenia
 Strongest predictors of CS for whole period –schizophrenia and bipolar and unipolar affective disorder
 Other disorders associated with increased risk – other depressive disorder, anxiety disorder, alcohol misuse (in females), substance misuse, and personality disorder

Professionals are obliged to take reasonable care to protect vulnerable charges from harming themselves. It is important to elicit whether suicidal thoughts are present or absent and if present if they are **active** (e.g. has settled personal affairs and stored tablets or bought a rope) or **passive** (e.g. feels like not going on but wouldn't do it because, e.g. of religious or family reasons).

Under the *Irish Suicide Act 1991* complicity in another person's CS or AS is a criminal act that may lead to a long term of imprisonment. The *Suicide Act 1961* in England and Wales removed CS and AS act from the list of crimes but left similar prohibitions regarding complicity in suicide (manslaughter under *British*

¹⁴⁷¹Addressed to statutory agencies.

¹⁴⁷² Creating problems for cases of suicide pacts and assisted suicides.

Homicide Act 1957). (Cf. suicide pacts later) Suicide *per se* ceased to be a crime in Ireland in 1993 (*Criminal Law [Suicide] Act, 1993*¹⁴⁷³). A study of Irish coroners' attitudes towards CS and its prevention (Farrow *et al.*, 2009), albeit one with a 62% response rate, suggested that they are open to discussing CS and prevention initiatives; about 1 in 4 see CS as a right or a justifiable resolution; and only 23% agree that CS is usually due to mental illness. The Catholic Church now allows full funeral rites and a Christian burial for suicides. Factors reported to increase the likelihood of CS are shown in the table. When reading this list one cannot escape the conclusion that one is reading a potted history of the rapid social changes that characterised the latter part of the twentieth century. This is suggested by increasing suicide rates in Russia¹⁴⁷⁴ where social and economic disintegration are important, as may gun ownership in some areas. (Webster, 2003) Men were often considered more likely to choose highly lethal methods of suicide such as hanging, whereas women were considered more likely to opt for self-poisoning. However, according to the National Parasuicide Registry, (Allen, 2005) in 2001 the percentages of male and female suicides employing drowning or hanging were not dissimilar (see Hawton *et al.*, 2008¹⁴⁷⁵), and the figures for overdoses among parasuicides for 2002 did not support large differences between the sexes. Also, Biddle *et al.* (2008a) found that CS by hanging¹⁴⁷⁶ in England and Wales increased among young women since the mid-1990s and had overtaken self-poisoning as the most common method. Additionally, Värnik *et al.* (2008) examined suicide methods in Europe and hanging was the most common method among males (except in Switzerland where firearms was more common) and, in eight countries only (including Ireland) among females; firearms was the second most frequent method in five countries but it was the least common method in Scotland; and women were more likely to drown themselves than were men (except in Luxembourg).

European female suicide methods (Värnik *et al.*, 2008)

Hanging – most common method in 8 countries
 Poisoning with drugs - most common method in 5 countries
 Jumping from a height - most common method in 3 countries

According to Brendel *et al.* (2008, p. 733) the most common method of committing suicide for both sexes in the US is by firearm (50-60% of CS). Other common methods are shown in the table.

Most common methods of committing suicide in the US (Brendel *et al.*, 2008)

<i>Men</i>	<i>Women</i>
Guns	Guns
Suffocation	Poisoning
Poisoning	

Notes

Suffocation includes hanging; poisoning include ingestion of drugs
 Method of unsuccessful suicide attempt is a factor in determining prognosis, e.g. in Sweden the risk of completed suicide is higher for such violent methods as hanging, jumping, shooting or drowning than it is for poisoning (Runeson *et al.*, 2010)

Beautrais (2003) found that the same risk factors¹⁴⁷⁷ were common to CS and 'serious' AS in persons aged less than 25 years; they were discriminated by gender and method used; these findings are hardly surprising since the more serious the attempt the less likely is survival, i.e. 'serious' cases may be true failed suicides. McClure (1994) drew attention to a rising CS rate since the 1970s in England and Wales in males aged 15-

¹⁴⁷³ This allowed coroners to bring in a verdict of suicide for the first time since the act was no longer a crime.

¹⁴⁷⁴ Rates per/100,000: 26.4 in 1990, peak of 42.1 in 1994, 39.7 in 2001; 6 males for 1 female; highest rate in males 45-54 years; highest female rate in over 75s.

¹⁴⁷⁵ 28-year period of non-fatal hanging and strangulation: M:F ratio of almost 3:1; cases had high suicide intent, relatively low use of alcohol associated with the act, and high future CS; and females had more psychiatric care, personality disorder, and previous self-harm.

¹⁴⁷⁶ Hanging accounted for 5.7% and 47.3% of female CS among 15-34 year olds in 1968 and 2005 respectively, self-poisoning falling from 64.1% to 35.5% during the same time period.

¹⁴⁷⁷ Mood disorder, history of psychiatric care, stressful circumstances.

19 years.¹⁴⁷⁸ This was associated with an increase in hanging and poisoning with vehicle exhaust gas. The author suggested that psychosocial factors played a role in this worrying trend. Methods vary around the world and in different cultures and circumstances, e.g. young Indian women living in the UK during the 1970s-80s often chose self-burning. In fact, self-burning is commonest in schizophrenic patients and in Asian women¹⁴⁷⁹. Tobacco growers in parts of Brazil (which has a relatively low reported suicide rate: Mello-Santos *et al.*, 2006) often employ organophosphate pesticides to commit suicide whereas in Sri Lanka oleander seeds are often used for the same purpose. Sartorius (2001) points out that ingestion of phosphor-based insecticides comprise the main method employed by young Chinese women to kill themselves. Eddleston and Phillips (2004) and Li *et al.* (2008) call for efforts to reduce the availability of such highly lethal poisons.

Opinions differ about suicide and cancer, e.g. most likely soon after diagnosis (Bostwick & Rundell, 1999) versus rare or held as a late option. (Fawzy & Greenberg, 1999) However, the risk *is* increased relative to the general population. (Whitlock, 1986)

Risk factors may affect the sexes differently, e.g. a Danish national registry study (Qin *et al.*, 2003) found that males were more likely to kill themselves if they were single, unemployed or had a low income, but living in an urban area might be protective; females were protected by having a young child but experienced increased risk if they had a psychiatric disorder, lived in an urban area, or (to a slight degree) if they had a family history of suicide.

Economic crisis (Gunnell *et al.*, 2009) can have serious mental health consequences and the suicidogenic potential of job loss is not confined to those with a mental disorder. It is important that social welfare supports are sufficient to help people to weather the worst aspects of economic downturns and that society responds supportively to those who lose jobs or are financially compromised.

Intellectual disability *per se* does not seem to increase the risk for CS, and being a male with intellectual disability might reduce the risk somewhat. (Popper *et al.*, 2003, p. 885)

Factors affecting completed suicide (CS) rates¹⁴⁸⁰

Suicide is the endpoint of the convergence of multiple influences acting on a person and on the society he or she lives in. Influences on population-level CS (e.g. stable, cohesive society) as distinct from individual-level CS will often be different (e.g. depression, alcohol¹⁴⁸¹). Genetic/familial transmission of suicidal behaviour appears to be independent of psychiatric disorder transmission. (Brent *et al.*, 1996) Women are diagnosed with depression more often than men but men, in most countries, commit suicide more often than women. Most depressed people do not kill themselves. The same parasuicidal act may have different implication in different people, e.g. trivial acts in the elderly must be taken very seriously. (Harwood, 2008, p. 557) In order to weigh risk for CS, risk factors should be considered in aggregate and viewed within the context of an individual patient's life circumstances and experience. (Kutcher & Chehil, 2007, p. 5)

Correlation and risk factors are not synonymous with causation. The list of risk factors is potentially legion and individual cases will vary in the importance of each factor. TCAs may be lethal in overdose but many authors feel that they prevent many more than they cause. Some TCA deaths may be due to underdosing by the prescriber, non-compliance, or lack of efficacy. Newer drugs might be given to people at risk of overdosing, but older drugs might be given to the severely depressed. One reason for the finding of increased suicidal behaviour in the first weeks after prescribing an antidepressant may be the lack of an immediate lifting of mood. (Jick *et al.*, 2004) However, it may be that most of these people were not taking the antidepressant. (Isacsson *et al.*, 1994) In part because of the significant methodological issues involved, (Simon, 2006) authorities differ on whether antidepressants reduce suicide rates, (Rihmer, 2001;

¹⁴⁷⁸ This must be seen against an overall trend of decreasing suicide rates in England and Wales across the 20th century. (Gunnell, 2005)

¹⁴⁷⁹ Women and girls in Afghanistan may self-immolate in order to escape forced marriage or violence/abuse. (Raj *et al.*, 2008)

¹⁴⁸⁰ From the literature.

¹⁴⁸¹ Power and Brophy (2008) found that CS rates in older adults during 1975-2005 increased and decreased in Ireland and the UK respectively and suggested that increased alcohol intake as well as a higher level of depression might account for this disparity.

van Praag, 2005)¹⁴⁸² and any tendency to increase such rates may differ between children and adolescents (an increase) and adults (no increase).(Olfson ea, 2006) As pointed out by Brent (2007), it is more likely that suicidal behaviour leads to treatment than that treatment causes suicidal behaviour. Problem-solving abilities, tolerance levels for stress, life events, locus of control, and other factors must interact to push someone to suicide, whether or not they are depressed.(Chiles & Strosahl, 2005, p. 65) Also, as stated by Goldney and Beautrais (2007, p. 525) individuals with few reasons for living are more like to choose CS irrespective of mental status. CS in rural south India (Manoranjitham ea, 2010) may be more related to psychosocial stress and social isolation than to psychiatric morbidity. Preventive factors (stigma, fear of death/suicide, cultural/moral/religious issues, family/child responsibilities, pregnancy, support network, survival/coping skills [e.g. non-violent resolution of conflict], access to help, treatment adherence) are more comfortable for a patient to discuss with a mental health professional than are risk factors and thus may be given excess weight by the evaluating clinician.(Simon, 2008, p. 1642) Most studies of CS come from *Europe* (UK and Scandinavia in particular) and *North America*, many studies use *chart diagnoses* of admitted patients, and use of *different diagnostic manuals* renders comparisons problematic.(Bertolote ea, 2003)

Increasing

Abortion

Absence/retirement of significant mental health professional

Access¹⁴⁸³ e.g. farmer and firearms¹⁴⁸⁴, pharmacist/doctors/nurses and tablets/expertise (Agerbo ea, 2007), suitable sites (e.g. The Golden Gate Bridge in San Francisco¹⁴⁸⁵ and, in Seattle, the ‘Aurora’ [George Washington Memorial] Bridge: Zarkowski, 2008; Blaustein & Fleming, 2009, 2010)

Acceptability of suicide by society/culture¹⁴⁸⁶

Adjustment disorder – interval to CS may be brief (Runeson ea, 1996)

Age¹⁴⁸⁷ – 60% of CSs in 1950 were > 45 years old, falling to 45% in 1998 (McKenzie ea, 2003) Children do not grasp the finality of death.

Agitation/anxiety/akathisia

AIDS - the suicide rate has been put at 60 times the expected rate; risk factors include depression, social isolation, poor social support, stigma, abandonment, substance abuse, co-morbid psychiatric disorders, employment or financial difficulties, unrelieved pain, and delirium. The situation may have improved since the introduction of HAART.(Keiser ea, 2010)

¹⁴⁸² Silverman (2003) reported that the US CS rate fell by only 1.2/100,000 between 1901 (11.8/100,000) and 2000 (10.6/100,000). One cannot confidently therefore conclude that treatments for depression do not work or at least prevent CS because we can't be sure of the statistics, antidepressants relieve depression but the patient may not be taking them (or may take them in excess) at the time of death, and whilst similar findings were reported for TB (no effect of streptomycin or BCG on declining rates) no one would seriously accept such arguments as favouring non-intervention.

¹⁴⁸³ Carrying firearms also increases the risk of being murdered.(Tanne, 2005)

¹⁴⁸⁴ Within the US laws governing access to firearms by people with mental illness/substance abuse are not uniform.(Norris ea, 2006) Legally restricted firearm availability in Austria reduced gun-related suicide and homicide.(Kapusta ea, 2007)



¹⁴⁸⁵ Golden Gate Bridge counselling offer. Putting up barriers (e.g. at Bloor Street Viaduct in Toronto) may merely lead to a shift to a different jumping point.(Sinyor & Levitt, 2010)

¹⁴⁸⁶ Seneca viewed CS as ‘the only permitted expression of freedom and autonomy’.(Porter, 2003, p. 4)

¹⁴⁸⁷ The elderly are, in general, relatively physically frail/non-resilient, more often have a number of somatic disorders, have greater access to prescribed medications, are more socially isolated (less likely to be found) and are poorer, and are more likely to be decisive (planned, resolved, lethal) and give less warning, compared to younger people.

Alcohol abuse/dependence¹⁴⁸⁸ - 3-4% in hospital-treated cases commit CS, especially if there is recent loss of a close emotional relationship, or if the patient is male, highly dependent on alcohol, has a long history of drinking, low mood, poor physical health, or recent poor work record. However, Harriss ea (2005) found high suicide intent scores to correlate with 'an absence of alcohol misuse' in males! Alcohol-dependence in sub-Saharan Africa is a major contributor to CS.(Ndosi, 2006) Walsh (2008) estimated that 1 in 6 CS is alcohol-related. An Irish study found 56% of CS tested positive for alcohol, rising to 92% in the under 30s. (IMO Position Paper, 2008, p. 5)

Antidepressants¹⁴⁸⁹ Jick ea (1995) found that only 1 in 7 people who killed themselves while on antidepressant treatment used the drug to kill themselves. Jick ea (2004) found no difference in suicidal behaviour between fluoxetine, paroxetine, amitriptyline, and dothiepin and BZDs and Tauscher-Wisniewski ea (2007) found no association between fluoxetine treatment for adults with various non-major depressive disorder diagnoses. Between 1971-88 TCAs accounted for <4% of all CS in Ireland. A 1995 UK GP study found that antidepressants caused 14% of CS but the risk was similar for a wide variety of agents, including mianserin and trazodone. Most lethal TCAs in overdose are dothiepin¹⁴⁹⁰, amitriptyline, imipramine and trimipramine. Of 4162 drug-related suicides in England & Wales during 1997-9, 22% involved TCAs alone, 18% co-proxamol alone, and 9% paracetamol alone.(Hawton ea, 2003a) During 1998-2000 in England and Wales, 80% of deaths from antidepressants were suicides¹⁴⁹¹.(Cheeta ea, 2004) Gibbons ea (2005) found that whilst new antidepressants and TCAs were associated with lower and higher CS rates the aggregate nature of these US data precluded a direct attribution of cause. Tiihonen ea (2006a) found that being on an antidepressant was associated with a marked risk of AS but also a greatly reduced risk of CS, the authors attributing the latter to the use of SSRIs. However, according to Reseland ea (2006) some countries may have experienced a fall in CS before the rise in antidepressant sales. Dumais ea (2005a) found that impulsive-aggressive personality disorders and alcohol abuse/dependence were independent predictors of CS in men with major depression. Hawton ea (2003c) looked at 300 cases of CS/probable CS in people who presented to hospital after deliberate self-harm (DSH) and found that the risk in the first follow-up year was 0.7%¹⁴⁹², 1.7% after 5 years, 2.4% at 10 years, and 3% at 15 years; males were at greater risk than females and risk for both sexes increased markedly with age at first presentation. Zahl and Hawton (2004) followed up deliberate self-harm (DSH) cases and found that 39% repeated DSH; repeaters were at greater relative risk of CS than single episode cases, especially for females. Cooper ea (2005) conducted a prospective study (1.9.97-31.8.01) of A&E DSH attenders and found a 30-fold increase in suicide risk, the standard mortality ratio (SMR) being much higher for females, and CS was particularly likely in first 6 months after index episode.¹⁴⁹³ Escalating severity of self-poisoning episodes puts people at high risk of CS.(Carter ea, 2005) Juurlink ea (2006) found that the elderly had an increased rate of CS during the first month of therapy if started on SSRIs, but the absolute risk is low¹⁴⁹⁴. Hall (2006) examined the relationship between SSRIs and suicide risk and concluded that any increased risk in adults may not be specific to SSRIs and is very small and outweighed by benefits; the risk-benefit ratio is less certain in children/adolescents (except for fluoxetine), although any risk is small and short-term (Dubicka ea, 2006; Bridge ea, 2007); and one should monitor suicidal ideation¹⁴⁹⁵ during the first few weeks of treatment. Gibbons ea (2006) found that higher prescription rates for SSRIs were associated with lower CS rates in children and adolescents. Gibbons ea (2007b) showed that restricting SSRI use in young people increases suicide rates. The finding of an excess of AS and CS in patients on venlafaxine (Rubino ea, 2007) was distorted by non-adjustment for confounders (Cipriani ea,

¹⁴⁸⁸ See Kølves ea.(2006)

¹⁴⁸⁹ See Edwards (2005) and Simon ea.(2006) The person may use another person's tablets. Possible disinhibition, possibly early return of volition. No evidence that TCAs lead to murder although there are published suggestions of released aggression.

¹⁴⁹⁰ A drug of abuse in Dublin during the 1990s.

¹⁴⁹¹ TCAs accounted for more drug mentions than other antidepressants and SSRIs were safer; SSRI-related deaths were most often (93%) associated with taking other drugs as well, esp. TCAs (24.5%); combination deaths also often associated with a history of drug misuse.

¹⁴⁹² 66 times the general population annual risk of CS.

¹⁴⁹³ Discovery avoidance, not living with close relative, past psychiatric treatment, self-mutilation, alcohol misuse, and physical disorders were independent predictors of future suicide.

¹⁴⁹⁴ Is this idiosyncratic or an artefact of matching a higher risk patient with an SSRI?

¹⁴⁹⁵ Borges ea (2006) conducted a household survey of adults and found 12-month prevalence estimates of suicidal ideation, plans and attempts to be 2.6, 0.7, and 0.4% respectively.

2007) such as diagnosis, comorbidity, dosages, adherence, and depression or suicidal ideation before going on the drug.

Anti-epileptic drugs – European and US reviews suggest that such agents may be associated with a small risk of suicidal thoughts and behaviour (Irish Medicines Board, 2009)

Anti-viral drugs – reports from Japan of delirium, convulsions, encephalitis, and suicide in patients receiving oseltamivir (Tamiflu) may be due to the drug or to a high rate of flu related encephalitis in that country (Maxwell, 2007)

Availability, e.g. household or industrial products; paracetamol caused >150 deaths annually in UK in early 1990s

Birth (of self) during April to June, especially for females (Salib & Cortina-Borja, 2006); low birth weight (Riordan ea, 2006)

Calcium channel blockers (not confirmed in a small sample study)

Cancer – especially of head and neck; prostate cancer in older males (Llorente ea, 2005¹⁴⁹⁶)

Certain days/dates, e.g. Mondays, start of a month, New Year's Day

Cholesterol lowering drugs (controversial - possible reduced central 5-HT density or missed alcohol abuse)

Coal gas

Command hallucinations

Cosmetic breast augmentation (Sarwer ea, 2007)

Cerebrovascular accident (especially younger people and women in a Danish study)

Divorce (may have different effects in different countries)

Early stages of bipolar disorder (BP) – or alcohol abuse and deteriorating function in BP (Dutta ea, 2007¹⁴⁹⁷)

Economic depression/excess borrowing (e.g. Wall Street Crash in USA or South Korea and Japan in the late 1990s or charcoal burning¹⁴⁹⁸ in post-transition Hong Kong)(e.g. Chan ea, 2005); social fragmentation may be more important than poverty (Whitely ea, 1999); Japanese middle-aged male CS may be a show of personal responsibility and remorse (*inseki-jisatsu*- responsibility-driven suicide) for economic problems (Takei & Nakamura, 2004); in Australia, male CS rates increased with markers of economic adversity (opposite effect in females) and younger person CS rates increased with higher housing loan interest rates (opposite in older people)(Berk ea, 2006)

Epilepsy

Family (Qin ea, 2002) or spousal (Agerbo, 2003) history of mental illness

Females – very high CS rate in rural southern India (Aaron ea, 2004); female medical students/doctors (Schernhammer, 2005); older women of South Asian origin in England and Wales (McKenzie ea, 2008); younger female prisoners in England and Wales (Fazel & Benning, 2009)

Fundamentalism/suicide terrorism: (Salib, 2003a) a receptive mind plus the right circumstances, e.g. poverty, sense of injustice or a callous and charismatic leader

Genes. CS 6 times more concordant in MZ twins than in DZ twins – what is inherited? depression? SSAT, the rate-limiting enzyme in polyamine metabolism, might be important in suicide and depression, with higher frequency of SSAT342C allele among suicide cases in a study of French Canadians.(Sequeira ea, 2006) Rap-1¹⁴⁹⁹ was found to be reduced in prefrontal cortex and hippocampus of depressed CS cases.(Dwivedi ea, 2006) BDNF G196A and 5-HTT-LPR polymorphisms were found independently to

¹⁴⁹⁶ Retrospective study of men aged at least 65 years who resided in South Florida during 1983-93. Of 667 CSs 20 cases had prostate cancer (3% of total male CS sample). Risk of CS in males with prostate cancer was 4.24 times that of an age- and gender-specific cohort. Clinical correlates were depression in 70%, diagnosis of cancer within 6 months of death (80%), physician visit within 1 month of death (60%), and being foreign-born (70%).

¹⁴⁹⁷ These authors found a standardized mortality ratio (SMR) for CS of 9.77 in BP. They traced 98.3% of their sample.

¹⁴⁹⁸ Barbecue charcoal burning as a method of suicide rose from 2% to over 26% of all CS between 1998 and 2003 in Hong Kong.(Yip ea, 2010)

¹⁴⁹⁹ Rap-1 is a substrate of PKA.

increase risk of suicidal behaviour in BP (Vincze ea, 2008); reduced BDNF expression in CS cases may be epigenetic (Keller ea, 2010)

Grief/bereavement: widowed at highest risk in days following loss, risk falling over the first year (Ajdacic-Gross ea, 2008)

Gun availability¹⁵⁰⁰ (especially USA; having a gun at home or for work/sport; removal of guns may only reduce CS among those who would have used a gun)

Haemodialysis – the CS rate is increased times among end-stage renal disease patients and those on haemodialysis (e.g. Brendel ea, 2008, p. 735) but not all patients to withdraw from treatment are suicidal (Levenson, 2008)

High homicide rate – also, offspring of psychiatric inpatients are more likely to die of homicide, CS, and open verdicts by poisoning (Webb ea, 2007)

High risk/low rescue situations: lethality of past self-poisoning (Owens ea, 2005)

Hopelessness - more predictive of eventual [not immediate] CS (Chiles & Strosahl, 2005, p. 11); Beck Hopelessness Scale identifies those at high risk of CS but the magnitude of the risk is not as high as previously reported, and low specificity reduces its usefulness in therapeutic targeting of self-harm repeaters (McMillan ea, 2007)

Hot weather (Page ea, 2007)

Immigrants, e.g. women born in Indian subcontinent living in Britain; loss of privileges among Russian minority in Estonia (Värnik ea, 2005)

Impulsive-aggressive traits – may be more relevant in younger people (McGirr ea, 2008)

Inpatients¹⁵⁰¹: AWOL; improvement clinically in absence of change in situational factors; partial alleviation¹⁵⁰² (may be seen as manipulative or complaining and so lose support); Qin ea (2005) found that hospitalised Danish suicides were associated with the periods just after admission¹⁵⁰³ and discharge, affective disorder, and brief hospital stay; Hunt ea (2009), apart from finding that the early post-discharge period was one of high risk for CS (43% occurred within 1 month and 47% of these died before first follow-up appointment), found risk (history of self-harm, primary diagnosis of affective disorder, a recent last contact with services and expressing symptoms at last staff contact, discharge AMA, and missing last appointment) and protective (involuntary status [for treatment] at last admission, enhanced aftercare) factors for CS

Insulin sensitivity¹⁵⁰⁴ (see Lawlor ea, 2003)

Intercountry adoption?

Internet advice¹⁵⁰⁵ on suicide and how to do it (cybersuicide)!(Biddle ea, 2008b; Coombes, 2008) A suicide video is available in Oregon.

¹⁵⁰⁰ The American Second Amendment in its Constitution preserves the right to bear arms but this dates from the early days of independence and the need for 'a well regulated Militia'. (Tushnet, 2008; Miller & Hemenway, 2008) Brady *Handgun Violence Prevention Act* (1994) in USA requires licensed firearms dealers to initiate check on background of people seeking to buy a handgun and to observe a waiting period between application and handgun delivery. However, as the 2007 Blacksburg (virginia) shootings amply demonstrated, it is easy to get a gun in the USA. (Anonymous, 2007) Firearms killed 30,143 people in the USA in 2005 (17,002 suicides, 12,352 homicides, 789 accidents) and wounded nearly 70,000. (Curfman ea, 2008)

¹⁵⁰¹ CS in psychiatric inpatients may have fallen during 1997-2003. (Kapur ea, 2006)

¹⁵⁰² Partial improvement as a factor in CS has been challenged by those who point out that suicidal tendencies wax and wane throughout a depressive episode.

¹⁵⁰³ Being off the ward with staff permission is a strong predictor of CS. (Hunt ea, 2007)

¹⁵⁰⁴ Possibly by lowering 5-HT and inducing depression.

¹⁵⁰⁵ E.g. *Alt Suicide* (ASH), *Satan Service*, and *Suicide methods.net*.

Location, e.g. high in deprived areas of Scotland/Scottish Highlands (highest alcohol consumption in Britain), (Boyle ea, 2005) Irish in Britain, Japan (school failure; Akita Prefecture has highest rate in Japan: Fushimi ea, 2006), New Zealand (failure to live up to 'macho' image and excel at rugby), some pockets in Hungary (possibly alcohol again¹⁵⁰⁶ – CS rate declined from 45.9/100,000 in 1984 to 31.7 in 1997 the decline being faster after 1990 when political changes began), and being Black or Native American in USA (alcohol and substance abuse, psychosis, depression and social loneliness in Native American Indians: Gaw, 2001, p. 33) – sex difference reversed in China (mainly young rural women according to Phillips R ea [2002] but older rural Chinese women also have an increased rate [Pritchard & Baldwin, 2002]); marriage was not protective against suicide among young rural Chinese women and being single but in a relationship is a risk factor for CS, religion/religiosity was not protective, and cultural conflicts (communism v Confucianism) and impulsivity were risk factors (Zhang ea, 2010); however, Tong and Philips (2010) found that suicide risk among urban residents with any mental disorder was more than double that of rural residents

Loneliness/social isolation/lack of social integration (Duberstein ea, 2004; Harriss ea, 2005); the effects of social fragmentation on CS rates are most marked in younger people (Whitley ea, 1999)

Low CSF 5-HIAA¹⁵⁰⁷ (probably relates more to impulsivity than CS per se; similar deduction from study of serotonin receptors in CS; low 5-HIAA (in impulsive violent criminals, arsonists and some violent alcoholics) and **HVA**; retrospectively, violent CS may be associated with lifetime history of aggression, impulsivity, substance abuse/dependence, and psychotic disorder (Dumais ea, 2005b)

Increased levels of 5-HT2A receptors, especially in prefrontal cortex¹⁵⁰⁸; other work suggests increase in 5-HT2A receptors in platelets, a reduction in 5-HT uptake, and less 5-HT transporter sites

Low cAMP binding to regulatory subunits of protein kinase A, as well as **reduced catalytic activity of protein kinase A**, in prefrontal cortex of CS victims who had suffered from major depression during life (needs to be replicated)

Low IQ (in Swedish males) (Gunnell ea, 2005) It has been stated that higher IQ may be a risk factor in people with schizophrenia. However, lower IQ may be a marker for liability to becoming a psychiatric patient in general and possibly having a personality disorder in particular (Urfer-Parnas ea, 2010)

Male sex (the classic case is the depressed older divorced male who does not practice his religion, drinks alcohol excessively, has no social supports, and suffers from a chronic painful immobilising physical illness; impulsivity in young males), despite the fact that females have a higher prevalence of depression. A Finnish prospective birth cohort study (Sourander ea, 2009) found that most males (but not females) who CS or made serious AS by adolescence/early adulthood had psychiatric problems by age 8 years (especially conduct disorder and internalising disorders)

Mania/bipolar affective disorder (BP) – BP at risk especially if young male, early phase of illness, abusing alcohol, and recently discharged from hospital¹⁵⁰⁹; suicide risk also increased in BP if in depressed phase, mixed state, or psychotic mania; absolute risk of CS for BP is about 193/100,000 (18 times the relative risk, i.e. compared to the general population), but 99,807 cases out of each 100,000 with BP will not kill themselves (Simon, 2008, p. 1638)

Media coverage of (a) suicides and (b) deaths of famous people (increased CS, especially female, in month following funeral of Princess Diana in UK – also increased parasuicide in females during same month); clustering of CS among mentally ill people may account for 10% of such cases (McKenzie ea, 2005)

Mefloquine (Lariam): antimalarial – rare reports of possibly-related suicidal ideation/CS - avoid/stop if history/emergence (depression, mood changes/instability, anxiety/panic attacks, confusion/restlessness-aggression-agitation/hallucinations/delusions), of psychiatric disorder (Irish Medicines Board, 2003)

¹⁵⁰⁶ Referring to the late 1980s, the historians Csorba ea (2003, p. 234) blame overwork and 'widespread alcoholism' as contributing to a low life expectancy in Hungary. Other writers refer to excess CS in both Finland and Hungary and, because these two populations share a single ethnic background, they suggest that this should be interpreted as a genetically determined phenomenon.

¹⁵⁰⁷ The 779C allele for tryptophan hydroxylase (TPH) gene (11p15-14) is associated with lower CSF 5-HIAA levels, again a finding that appears to correlate with impulsivity. (Nielsen ea, 1998)

¹⁵⁰⁸ There is evidence that recovered unipolar depression cases have increased 5-HT2A receptors (PET) and that this correlates with dysfunctional attitudes. (Bhagwagar ea, 2006) Individuals with TT/T or T/C genotype of the T102C polymorphism of the 5-HT2A receptor gene are more responsive to protective maternal nurturing than are those with the C/C genotype. (Jokela ea, 2007)

¹⁵⁰⁹ A study in Taiwan of CS among severely depressed patients (Lin ea, 2008) found that the mean number of days following discharge for CS was 29.9. Patients discharging themselves AMA were 2.85 times more likely to commit suicide than were those leaving hospital with the doctors' approval.

Miscarriage

Modern living, e.g. crime, illegitimacy, or low social cohesion with low marriage rates and increased marital separation rates (youth suicides)

Natural disasters (literature suggests some disasters such as hurricanes but not others such as storms – artificial? – most people exposed to disaster do not develop PTSD or other mental disorder [Bromet & Havenaar, 2002])

Occupation, e.g. farmer (in ROI and UK), caring professions (doctors and nurses: Agerbo ea, 2007), low job status (Agerbo ea, 2007), taxi driver, chef, tradesman, unemployed; farmers may take too low a dose of antidepressant, have insomnia treated and depression missed, not be treated at all, lack a close confidant, have work/financial problems, and have firearms which they know how to use¹⁵¹⁰; job classification changes and Meltzer ea (2008) found in England & Wales that in 2001-5 male CS numbers were highest in construction workers and plant/machinery operatives but rates were highest in professionals and agricultural workers whereas in females administrative/secretarial had the highest numbers with the highest rates in health/sport and fitness

Pain, especially chronic (Fishbain ea, 1991)

Panic/anxiety – Brendel ea (2008, p. 734) suggest that up to 20% of people with anxiety disorders kill themselves and hold that anxiety disordered people have almost the same suicide risk as do people with major depression, but some of this increase is accounted for by co-morbid alcohol/substance abuse and depression

Perinatal circumstances – higher maternal parity, mother < 20 years old, non-professional parents, low birth weight (< 2500 g) (Riordan ea, 2006)

Personality disorder - perhaps half or more of cases; especially dissociative, of whom 5% commit suicide; 3-8% in borderline personality disorder; history of adolescent emotional instability and conduct problems in an adult; McGirr ea (2009) suggest that familial transmission of CS and major depression, while partially overlapping, are distinct, and that cluster B traits and impulsive-aggressive behaviour represent intermediate phenotypes of CS

Physician-assisted suicide/euthanasia (O'Shea, 2000d)

Positive DST (Coryell & Schlessler, 2001): survival analysis showed estimated risk for eventual CS was 26.8% if DST abnormal v 2.9% if DST normal

Primary affective disorders (PAD): CS rate 30 times general population rate; ultimate CS risk of 15% in PAD seems high (Inskip ea [1998] put it as low as 6%)¹⁵¹¹; very high in psychotic depression; depression is diagnosed in over half of elderly CS in psychological autopsy studies (Harwood, 2008, p. 559); no difference in CS between depressives with/without melancholic features (Kessing, 2003)

Prisoners (especially if on remand, first week in prison, in receipt of a long sentence, high violence index offence/convicted of serious offence, history of psychiatric contact or suicidality, on psychotropic medication, drug dependence, 30 years of age and older¹⁵¹², single-cell accommodation, availability of ligature points in cells; 54 attempts at suicide in Irish prisons in 1999 resulting in 6 deaths)¹⁵¹³ It should be noted that release (especially if recent) from prison is associated with an increase in CS (Pratt ea, 2006, 2010; Frater, 2008) although certain groups may be at particular risk, e.g. history of self harm or alcohol abuse or having a psychiatric diagnosis.

Puerperium (associated with psychiatric illness; less common than previously – in fact the rate may have fallen below general population!)

¹⁵¹⁰ To kill sick stock.

¹⁵¹¹ The exact figure is debatable, e.g. van Praag (2005) states that 15-19% of people who were ever hospitalised for depression commit suicide and lower figures are reported for depressed outpatients. Gelder ea (2006, p. 410) accept the 6% figure. According to Nierenberg ea, (2001) the lifetime CS rate for severe major depression is 3-8%.

¹⁵¹² However, Fazel ea (2005) reported a real increase in English prison suicides, esp. in males aged 15-17. According to Frater (2008) the self-inflicted death rate in English prisons rose to 14.8 in 2002-3/100,000 prisoners, falling slightly to 11.1 in 2007-8. Prison suicides in England & Wales April 2002-March 2003 totalled 105 with 92 males and 13 females. Deaths from natural causes are also increased in prisoners. (Frater, 2008)

¹⁵¹³ Mullen and Lindqvist (2000) list certain factors likely to increase suicidal behaviour in prisoners: personality factors (hopeless, suspicious, non-trusting), history of self-damage, substances (intoxication/withdrawal), long sentence, guilt/self-blame, chronic painful or fatal disorders, and the environment (fear due to victimisation/intimidation, social isolation, lack of power to influence events, a Spartan milieu, lack of meaningful activities/boredom, and humiliation). See also Fruehwald ea. (2004)

Religion (private faith more protective than external observance, and church attendance is more protective than denomination; differences between Catholic and Protestant countries might relate to gross domestic product; Muslim countries are said to have low rates (not all data support this and violent deaths may have an element of suicide attached: Pritchard & Amanullah, 2007), but countries with religious sanctions are less likely to return rates to WHO)(Koenig, 1999; Dervic ea, 2004); Buddhist teachings are not clear on morality of suicide and suicide as part of samurai code are among factors that may operate in Japan (McCurry, 2008)

Retired status

Risk-taking behaviour in adolescence, including sexual activity

Schizophrenia¹⁵¹⁴ Perhaps 10% kill themselves, but Inskip ea (1998) put it at 4%; low CSF 5-HIAA may be a factor

Severe mental illness, e.g. non-affective psychosis in the older male

Shorter hospital stays

Socio-economic groups I & V - In Denmark, with no private service, a history of mental illness plus affluence increases CS risk); European men of low socioeconomic status at greater risk for CS – this appeared less relevant for women (Lorant ea, 2005); Rehkopf and Buka (2006), in a systematic review, found inverse relationship between CS rates and area socio-economic position

Spinal cord injury (depression important; lack of social contact and unemployment; less severe injury: Geisler ea, 1983; De Vivo ea, 1999)

Stigma (reduces help-seeking)

Stillbirth

Substance abuse (complex association, e.g. with cannabis [Lynskey ea, 2004])

Suicide among close relatives (Qin ea, 2002) including spouse (Agerbo, 2003)

Teenage pregnancy/offspring of teenage mothers (Olausson ea, 2004; Ekéus ea, 2006)

Terminal illness

Unmarried motherhood (also increased mortality from violence and alcohol)

Veteran (military) status – white, more educated, activities limited by illness, normal weight (> overweight) (Kaplan ea, 2007)¹⁵¹⁵

Visual impairment, neurological disorders, and malignancy in elderly Swedes (Waern ea, 2002)

Women employed outside the home

Possibly decreasing

Antidepressants (Olfson ea, 2003; Gunnell & Ashby, 2004), especially in older adults (Stone ea, 2009)

Antipsychotic treatment (Tiihonen ea, 2006b)

Apathy/avolition, e.g. in some cases of schizophrenia (Kutcher & Chehil, 2007, p. 19)

Certain dates, e.g. Christmas Day; a general reduction before and during all holidays in USA

Children (independent of social class and education), e.g. Norwegian mothers less likely to kill themselves the more children they have – but loss of a child, especially during first month after loss, can increase risk
Church support

Clozapine (not all sources agree – compare Sernyak ea, 2001; Meltzer, 2002; Meltzer ea, 2003; Duggan ea, 2003)

¹⁵¹⁴ The highest risk for suicide is soon after diagnosis and so CS rates may vary depending on when they are measured.

¹⁵¹⁵ Prospective population-based study in US – veterans twice as likely to kill themselves as non-veterans but just as likely to die from illness or 'external' causes (no increase in chances of being murdered or dying in an accident).

Collaborative therapeutic relationship and symptom improvement in BP (Ilgen ea, 2009)

Community psychiatric services (Pirkola ea, 2009)

ECT

Female sex

HAART for AIDS (Keiser ea, 2010)

Higher socioeconomic status (see O'Reilly ea, 2008)

Limiting pack sizes of paracetamol, salicylates and other OTC drugs following 1998 legislation in UK (Hawton ea, 2001a) and 2001 legislation in Ireland (Donohoe ea, 2006)

Lithium prophylaxis (even when affective disorder not controlled; possible anti-aggressive effect)(Kessing ea, 2005; Cipriani ea, 2005); suicidal behaviour occurs 2-3 times less often in patients on lithium compared to those on divalproex(Goodwin ea, 2003)

Lithium in drinking water (Ohgami ea, 2009)

Married/cohabitating, Married woman with children

Methadone (also use in overdoses)

Natural gas (replacing coal gas)

Parental support

Pregnancy

Student status

SSRIs?(Hall ea, 2003)

TCAs (higher prescribed doses have correlated with reduced suicidal behaviour)

Twins – this may reflect strong family ties(Tomassini ea, 2003)

War¹⁵¹⁶

Work

Neutral

TCAs

Increased antidepressant prescribing in Iceland 1975-2000.(Brugha ea, 2004;Helgason ea, 2004)

¹⁵¹⁶ **War and suicide:** Exceptions abound, e.g. police in Northern Ireland (New York City police do not have an increased suicide rate according to Marzuk ea, 2002), frontline soldiers at Stalingrad (the commanding general [Paulus] had to issue an order forbidding suicide as dishonourable: Roberts, 2009, p. 341), whole families in East Prussia during the Soviet advances e.g. see Hastings, 2004, p. 337; Davies, 2006, p. 342), diners in Dresden restaurant who were trapped after Allied bombing of February 1945.(Taylor, 2004, p. 352) and prisoners of war who seek death whilst trying to escape (suicide-by-escape: Roberts, 2009, p. 162). Suicide risk is increased among civilians exposed to 'friendly' bombardment (Beevor, 2009, p. 314) and inexperienced replacements in a combat zone (Beevor, 2009, p. 258). Jews who realised their role in organising fellow Jews for 'resettlement', civilians in France in 1940, (Vinen, 2006, p. 14) facing prosecution for war crimes (Stafford, 2007), monks burning themselves during the Vietnam War to make a politico-religious statement. However, the rate also fell during both world wars in non-belligerent countries like Switzerland. High rate of suicide in Sri Lanka during civil war where pesticides were readily available. Suicide declined briefly in Britain immediately following the crashing of 'planes into the Twin Towers in New York (Salib, 2003b) and following 7 July 2005 terrorist attacks in London.(Salib & Cortina-Borja, 2009) Suicide less likely among motivated paramilitaries.

Properly conducted trials in schizophrenia that use placebo (Storosum ea, 2003)

No urban/rural difference in Corcoran ea (2003)

Gestational age at birth¹⁵¹⁷ (Riordan ea, 2006)

Intellectual disability is not associated with an increase in CS (Simon, 2008, p. 1640)

Ovenstone and Kreitman (1974) divided suicides into a 'P' group comprised of sociopaths, drug addicts and alcoholics, were known to psychiatrists, were largely refractory to treatment, had long and unstable histories with chronic personal and social disorganisation, were in debt, had a criminal record, used drugs to kill themselves, told others what they were going to do before they did it, and committed suicide in the presence of other people, and a 'NP' group consisting of more stable personalities with shorter periods of instability who killed themselves because they could not adapt to acute stress, especially following loss of a loved person, were alone at the time, used lethal methods such as carbon monoxide and self-injury, and warned no one of the act. The P group had a history of parasuicide, whereas the NP group had no such history.

People under 35 years of age may be less likely to visit their GP in the months before suicide. They may not see talking about emotional issues to their doctor as appropriate. Also, suicide in this age group may be impulsive. Based on British coroners' inquisitions, many elderly CS may not be in contact with primary care, may receive inadequate treatment (e.g. antidepressant), and may infrequently be referred for psychiatric care. As many suicides in northern England were found to see a police officer in the last 3 months of their lives as had seen a mental health professional in the last 12 months. (Linsley ea, 2007) Emile Durkheim described four categories of suicide in 1897: egoistic (lacks significant interpersonal relationships), anomic (anarchy leads to a loss of social restraint), altruistic (dies for a common cause) and fatalistic (excessive restraints on liberty, e.g. POW camp). Suicide in Japan is now seen as being less honourable than it was in the 1940s.

Very high rates of CS have been reported in China.¹⁵¹⁸ Rates of depression were said to be low. Women commit suicide more often than men in China. (Phillips R ea, 2002) Yip and Liu (2006) argue that male Chinese CS rates are increasing and will surpass female rates eventually due, they believe, to increasing urbanisation.

Among 15-19 year olds globally, the countries reporting higher CS rates for females than males are China, Cuba, Ecuador, El Salvador and Sri Lanka. (Wasserman ea, 2005)

The *Werther effect*, called after one of Goethe's characters, refers to the influence of media coverage on the suicide rate. Whilst research shows some positive associations, the contribution is only part of a multifactorial aetiology, and the effect may be transient in some cases. Concern over the influence of media reporting of suicides has led to strong suggestions for more responsible reporting, the avoidance of dramatic portrayal and oversimplification of causes (e.g. leaving out mental health issues), and the need for a clear policy on internet 'suicide sites'. (Hawton & Williams, 2002)

The incidence of suicide in the medical profession is high. Females, as medical students and doctors, are disproportionately affected. (Schernhammer & Colditz, 2004) Various factors may affect female rates, e.g. single childless status and sexual harassment. (Schernhammer, 2005)

At-risk patients who seek seclusion should be carefully observed. Doctors who are being investigated or who have been suspended from the professional register have been noted to be at increased risk of CS in the US, UK and Ireland. (e.g. Ganly, 2004)

¹⁵¹⁷ Räikkönen ea (2007) found increased susceptibility to depressive symptoms at age 60 years in people with shorter length of gestation.

¹⁵¹⁸ Kleinman (2000) has suggested that family conflict, failure to give birth to a son, and 'loss of face' are important reasons for CS in China. Phillips and co-workers (Phillips MR ea, 2002b) interviewed the families and close associates of 519 CS's in China and used persons who died from other injuries as controls. The risk of CS increased as the number of risk factors increased. In order of importance these risk factors were high depression symptom scores, past personal AS, acute stress, low quality of life, high chronic stress, severe interpersonal conflict during the 48 hours before death, and previous suicidal behaviour in a blood relative or a friend. Females outnumbered males, rural villagers were over-represented, and victims were older than controls (mean in years: 48 v 43). Methods of CS included agricultural chemicals/rat poison (62% - often stored at home), hanging (20%), other poisons (7%), drowning (5%), jumping (2%), and other (4%). Negative life events such as economic problems and serious illness or injury did not differentiate the two groups (although both groups had an excess) and other events (childbirth, pregnancy [incl. unwanted], fines for exceeding birth quota, abortion, and sterilisation) were only somewhat more common in the female CS group (16% v 11% in female controls).

Children's ability to grasp the finality of death is usually developed sometime after their seventh birthday, the concept continuing to develop thereafter. Nevertheless, even younger children can have suicidal thoughts or even harm themselves deliberately.

About 20% of suicides leave a suicide note, the percentage perhaps being higher in the elderly. (Harwood, 2008, p. 558)

Most psychiatrists will experience CS among their patients. (Landers et al., 2010) At least a minority will experience depressed mood, insomnia and irritability as a result of such an experience. Nearly half will change the way they practice in various ways such as becoming more structured in their approach to patients or admitting more involuntary patients. A few will consider early retirement. Shock, fear of blame, grief, guilt, self-doubt, shame, anger, and a sense of betrayal are common. Colleagues, family and friends offer the best support. Other useful measures are team and critical incident reviews. These allow to learn and to improve our clinical management skills of such cases and to handle the aftermath better. The relatives of the deceased ('suicide survivors' in US) should be offered an early appointment wherein the tragic event can be discussed in an open, honest, uninterrupted and sympathetic manner.

Help needed by surviving relatives of CS (American Foundation for Suicide Prevention¹⁵¹⁹, 2007)

Acceptance and understanding of their troublesome feelings

Help to learn to accept guilt/anger

Help to work out self-blame for not preventing the death

Channelling intense, painful feelings into activities that help others, including suicide prevention

Epidemiology of CS

The Central Statistics Office for Ireland gets its information on CS from the investigating Garda (police) who gives his/her opinion on the cause of death on the confidential Garda Síochána (police force) Form 104 after a coroner's inquest has taken place. The coroner produces a Record of Verdict¹⁵²⁰ at the end of his/her deliberations.

Official suicide figures in Ireland may have underestimated the problem in the past (underreporting may still apply in India: Joseph et al., 2003). Reasons for missing CS include stigma and the need for criminal rather than civil standards of proof. The table provides suicide figures for the Irish Republic.¹⁵²¹ According to Chisti et al. (2003) Ireland has the fastest growing CS rate in the EU, this being largely a male phenomenon¹⁵²². However, according to the Irish Minister for Health, (Anonymous, 2004b) Ireland, with 10.2 suicides/100,000 people, came 17th out of 24 European countries, a figure below the European average of 14.9. Lithuania topped the list with 39.6 and Greece occupied the bottom with 3.1. According to Mullins (2005) the European Union experienced 58,000 suicides and 50,700 deaths from road traffic accidents (RTA) per annum respectively. According to the OECD report *Health at a Glance 2009* the Irish RTA death rate fell by 60% during 1970-2006 (OECD average = 58%).

Official suicide data, Republic of Ireland (ROI)

Statistics on CS have been kept since 1942. According to Walsh (2008) CS rates rose until WWI, fell until 1970, then rose slowly but this rise accelerated during 1990-2001 and then fell. He cautions against drawing too many conclusions about trends since numbers are small, especially for females. Also, figures vary because yearly summaries on vital statistics precede annual reports by 2 years. Walsh (2008, p. 55) makes the interesting proposition that Irish CS rates may have fallen when we exported people who killed themselves abroad and then rose when emigration declined and we welcomed immigrants from Eastern Europe. (see Harding &

¹⁵¹⁹ Founded 1987: 120 Wall St, 22nd Floor, New York, NY 10005 or 888-335-AFSP or www.afsp.org.

¹⁵²⁰ This gives identity of deceased, date/place/circumstances of death, and whether death was accidental, homicidal, suicidal, or undetermined whether accidental or not.

¹⁵²¹ The Irish suicide rate rose from 2.38 to 10.69 per 100,000 population from 1945-95. The rate for men of 65 or more years rose from 9.4 to 17.9 between 1976 and 1993, and was 17.17 in 1995 with women at 4.32. Between 1995-9 18 males and 3 females aged 5-14 years committed suicide. Over the same period there were 1,799 male CS and over 400 female CS. Hanging accounted for 857 male suicides and 104 female suicides, while drowning was the method used by 376 males and 141 females. Unreported cases for that period are suggested to run at 5%.

¹⁵²² The male rate being similar to the EU average while the female rate remained low.

Balarajan, 1996) There is some evidence from the US that a disposition towards mood and anxiety disorders may be acquired early in life by spending ones childhood in the USA.(Breslau ea, 2009)

Year	Number of suicides	Comments
1945	71	Not much faith can be placed in early statistics
1965	51	Lowest on record
1970	52	1.75/100,000 in 1970 v 7.87 in 1983; 44M:8F
1989	255	The 1988 rate for men was 12.2/100,000 and 3.4 for women; the overall rate for 1988 and 89 being 8.0
1990	311	Rate = 9.0; 6 fold increase over 20 years previously; 4,114 suicides over past 20 years, an average of 206/year; >3M:1F
1991	318	235M:66F; rate in ROI was 9 versus 8.3 in UK; increase in young males
1992	353	Rate = 10.2; 295M:85F
1993	357	
1994	353	280M:73 (rate = 9.89/100,000 – not distributed evenly, e.g. Mayo = 11.59); 6 aged 5-14 years; biggest group (77) = 15-24
1995	383	86 in 25-34 age group, 82 in 15-24, and 4 in 5-14
1996	378	310M:68F
1997	433	355M:78F; 8 aged 5-14; 103 aged 15-24; 99 aged 25-34 ¹⁵²³
1998	514	Rate = 14.1/100,000; 433M:81F; highest numbers in 20-29 group ¹⁵²⁴
1999	439	Rate = 12.1; 349M: 90F
2001	448	80% were males
2002	451	Rate = 11.5/100,000 (343 deaths from RTAs; 31 from homicide, 77% being males) ¹⁵²⁵
2003	444	3 inpatients committed suicide ¹⁵²⁶
2005	432 ¹⁵²⁷	354M:78F; M<35 yrs = c. 40%
2006	409	Rate = 9.6/100,000; 78% M and 22% F (Death from RTAs = 285, a rate of 6.7/100,000); if 66 undetermined deaths are added the figure becomes 475 (11.2/100,000)
2007	* ¹⁵²⁸	
2008	424	CSO
2009	527	CSO – highest figure to date ; 80% male; 40% of CS were < 45 years old

Notes: Violent methods increasing. Main rise is in young men. Rural > urban. CS rates for ROI can vary with source, e.g. compare above with McGuinness.(2007) CSO: Central Statistics Office

In 1991, CS was the eight leading cause of death in the US, at 30,000 deaths per year, with the greatest numbers made up by young adults and the greatest rates being among the elderly, especially elderly white males. In Ireland deaths from CS equalled those on the roads in 1995. In 1992 and 1997, the number of CS in France and the Republic of Ireland respectively exceeded the number of deaths from road traffic accidents (RTA) for the first time.¹⁵²⁹ In the Republic of Ireland in 2001 there were 448 suicides and 357 deaths from RTAs. Despite the increase in CS relative to RTA-related deaths the 2010 funding for the National Office of Suicide Prevention and the Road Safety Authority are €5.1 million and €40 respectively. Gunnell ea (2003) found that succeeding generations of UK males born after World War Two experienced increasing rates of CS at all ages, a finding which has also been recorded in Canada and the US. According to Gunnell and Middleton,(2003) whilst the standardised suicide rates fell by 18% between 1981-98 in

¹⁵²³ Rate in ROI in 1997 = 11.94/100,000 (Hungary, 38.6; Mexico, 2.3); there were 31,605 deaths in ROI in that year and 1.4% were by suicide. Webster (2003) states that Lithuania has the highest rate (51/100,000) worldwide.

¹⁵²⁴ Highest recorded figure to that date. Highest rate in Kerry (23/100,000) and lowest in Longford (3.3) – figures for counties vary with the year but Eastern Region tends to be relatively low.

¹⁵²⁵ 111 suicides (11/100,000 pop.) in ROI in quarter 2 of 2003 = 30% of deaths in 15-24 age group and one-quarter of deaths in 25-34 age group; males, 83%; females, 17%.

¹⁵²⁶ A significant percentage were on leave or AWOL. Compare with 3 in 1866 when hospitals (asylums) were closed environments.

¹⁵²⁷ 431 is an alternative figure.

¹⁵²⁸ Different sources give widely differing figures for 2007. The National Office for Suicide Prevention (www.nosp.ie) Annual Report (2008) states that 481 CSs (given as 460 in Anonymous [IMN, Sept. 15, p. 8], 2008!) were recorded in 2007 'slightly lower than in previous years', which makes no sense when placed beside CSO figures for CS. A glance at the graph in that publication shows very little change in CS rates from 1980-2005, whereas males and females had highest rates in 1998 with a tendency to decrease thereafter, but the line representing the 1998 peak does not reflect these changes! Provisional figures from the National Office for Suicide Prevention suggest that CSs fell to 424 in 2008. An OECD report (*Health at a Glance 2009*) gives the mortality rate from suicide for Ireland as 8.9/100,000 (the OECD average being 11.1), indicating a continued decline since 2003.

¹⁵²⁹ Alcohol excess is common to many CS cases and RTA (and domestic) fatalities in Ireland.(Bedford ea, 2006)

England and Wales, the potential years of life lost before age 65 years increased by 5%. The UK suicide rate in 2007, a record low, was 7.5/100,000 population; there was a sustained decline in CS rate among males aged less than 25 years; CS among psychiatric inpatients fell from 216 in 1997 to 136 in 2006; and CS in prisons fell from 65 in 1997 to 60 in 2008.

Young male CS in England & Wales (Biddle ea, 2008a)

Rates more than doubled from early 1970s to the 1990s

Rates peaked in 1990 for 15-24 year olds and then fell

Rates peaked in 1998 for 25-34 year olds and then fell

In 2005 rate in males aged 15-24 = 8.5/100,000 (peak of 16.6 in 1990)

In 2005 rate in males aged 25-34 = 15.7/100,000 (peak of 27.9 in 1998)

According to Webster (2003) the average CS rates in Western Europe and North America were 5 and 4.1/100,000 respectively. Rising suicide rates in young males is a global problem.(Wasserman ea, 2005) However, CS rates in young men fell steadily in England and Wales since the 1990s, reaching their lowest point for almost 30 years in 2005¹⁵³⁰.(Biddle ea, 2008a)

CS and self-mutilation are coded in DSM-IV-TR under an F code: 'other conditions that may be a focus of clinical attention'.

Prediction of CS

'Unless and until significant new risk predictors are developed and evaluated, it is unjustified to assume that a suicide can be predicted'.(Chiles & Strosahl, 2005)

'...more important than constructing a list of risk factors is establishing the meaning of the patient's current life experiences to that person at that point in time'.(Harwood, 2008, p. 561)

'No form or protocol can encompass all possible risk factors'.(Simon, 2008, p. 1638)

Predicting suicide is very poor,(US Preventive Task Force, 2004) even if cases are seen shortly before death,(O'Shea ea, 2000; Carroll-Ghosh ea, 2003; Dubovsky ea, 2003) and even if they are inpatients.(Powell ea, 2000) We are better at predicting immediate risk than telling the future. CS is rare and suicidal ideation is common, leaving us with a base rate problem. Perhaps one percent or more of parasuicides go on to kill themselves, but which 1%?¹⁵³¹ Risk factors retrospectively identify groups of people who have killed themselves rather than prospectively identifying individuals who may do so. They have a high sensitivity but low specificity, spewing out many false positives.¹⁵³² Castle ea (2004) found that thoughts about death, thinking about suicide, bizarre behaviour and making violent threats distinguished CS from accidental death in both blacks and whites; reports of community complaints and problem drinking were associated with CS in whites more than in blacks; and no variable conferred greater risk for CS in blacks than in whites. Of note, racism data were not available to the researchers. Also, Gunnell ea (2004) found that less than 0.5% of people who experience suicidal thoughts go on to CS. Also, whilst past AS has a higher standardised mortality ratio than any psychiatric disorder, physical illness, or substance-related disorder,(Simon, 2008, p. 1641) most people who kill themselves have no known history of AS.(Malone ea, 1995) Human beings are complicated and cannot be reduced to mere statistics; what an event means emotionally to one person at one point in time can have a totally different meaning at another time, and the same event can have very different meaning for different people. It is important to ask patients what reasons they have for living.

In a psychological autopsy study of 85 suicides aged over 65 years of age at death, Waern ea (2002) found that 97% (v 18% in living comparators) had at least one Axis I diagnosis, commonly recurrent major depression or substance use disorders. Increased risk was also associated with minor depression, dysthymic disorder, psychosis, single episode major depression, and anxiety disorder. Comorbid Axis I disorders were found in 38% of suicides (15 subjects) with major depression. Cavanagh ea,(2003) in a systematic review of psychological autopsy studies, found a median of 91% of suicides (varying widely depending on

¹⁵³⁰ The authors explain this as being partly due to catalytic converters (that oxidise CO to CO₂), but point out that all major means of CS have declined.(Biddle ea, 2008a) Less unemployment and a falling divorce rate may be other positive factors.

¹⁵³¹ According to Owens ea (2002) the non-fatal repetition rate after one year is 15%; the risk of CS after 1 year is 0.5-2% and above 5% at 9 years. Jenkins ea (2002) and Suominen ea,(2004) have shown that the risk for CS following parasuicide persists for many years, even for the entire adult lifetime.

¹⁵³² It has been shown that for every 100 suicides predicted the forecast proved wrong in 97 times!(Pokorny, 1983)

methodology) had a 'mental disorder' (authors unable to draw conclusions about individual disorders or sociological variables) and comorbid substance abuse was a major risk factor.

Predictors of AS or CS may differ between the sexes.¹⁵³³

Questionnaires are most useful for research when used in a population for long-term prediction, but do not replace individual clinical assessment. Beck's scale for suicidal intent (Beck ea, 1974) is widely used in clinical practice but seems to show poor agreement with clinician's rating of the same phenomenon.(Keeley ea, 2002) Harriss ea (2005) found this scale most predictive for the first year and for females.

Important in determining suicidal intent *at the time of the act of self-harm*

Premeditation - buying a rope, securing a flat unknown to others, saving up tablets, getting tablets from many sources

Secrecy - precautions against discovery

Not alerting potential helpers

Being alone

Final acts - writing a will, insurance cover, a suicide note

Violent or aggressive act

Low lethality act believed by the person to be lethal

It is important to consider suicidal intent even in very young children.(Connolly, 1999) About 46 Irish children under the age of 14 years commit suicide annually, the rates¹⁵³⁴ (per 100,000) for 5-9 year olds and 10-14year olds being 0.1and 1.0 respectively.

Potential warning signs of suicide in adolescence

Withdrawal from family/friends/wider social interaction

Loss of interest in formerly enjoyed activities

Major functional changes (social, scholastic, and occupational)

Major changes in behaviour/personality

Self-neglect (hygiene, clothes, make-up) or self-deprecation

Parting with prized possessions

Low mood/sadness/despair/hopeless or irritable/aggressive/angry or poor emotional control

Preoccupied with death or suicide of others (as shown in words, reading, writing, drawing, or TV programme choice)

New/increased impulsiveness/risk-taking

Large weight increase/decrease

Poor sleep

Alcohol/substance use

These 'signs' must be weighed in the context of the individual's life story and circumstances as individually they may reflect normal adolescence. Do the adolescent's peers view their friend as having changed significantly or being ill?

Extended suicide

Talk about harming someone else who is also believed to suffering e.g. child, parent, or spouse

Passive suicide

Kills self though deliberate neglect, e.g. transplant patient stops immunosuppressant (e.g. cycloserine)

Passive death wish

Wishes to die but not by own action

Suicide pacts (O'Shea ea, 2000)

¹⁵³³ Looking at people with major depression, Oquendo ea (2007b) found that a family history of suicidal acts, past drug use, borderline personality disorder, and early parental separation increased risk in males, whereas prior AS (incl. lethality of same), suicidal ideation, subjective depression, less reasons for living, borderline personality disorder, and cigarette smoking increased risk in females.

¹⁵³⁴ Based on figures released by National Office for Suicide Prevention in their 2008 Annual Report.

Agreement between at least two people to commit suicide together¹⁵³⁵ account for 6/1,000 suicides in England and Wales (rate of 6/10,000,000 people of at least 15 years of age)
 May be between married couples or, less commonly, between family members
 Typical case is female, 60 years old, married, high social class
 Majority either mentally ill or have history of mental disorder
 Commonest diagnosis is depression
 Alcohol is not a big factor
 Have been arranged between strangers over the internet in Japan - details worked out via special suicide websites (Rajagopal, 2004)
Dyadic deaths ('murder-suicides': O'Shea ea, 2000)
 Person kills someone else before ending own own life¹⁵³⁶
 Uncommon
 Perpetrator usually male
 Victim usually female
 Commonly share a close relationship
 Motivation varies but includes money worries and emotional rejection
 Barraclough and Harris (2002) looked at homicide followed by suicide in England and Wales during the period 1988-92 and that this was mostly a 'family affair' - men, mainly of low socioeconomic status, kill their kin and women (typically premenopausal) kill their young children - a few men kill strangers

Almost 1% of people discharged from UK psychiatric in-patient facilities kill themselves over the next 12 months, accounting for 10% of CS. According to Crawford,(2004) the classic post-discharge CS is a non-White unemployed male aged over 45 years who lives alone and is socially isolated; he was recently admitted for the first time, had suicidal ideas at the time of admission, was diagnosed as having depression or affective psychosis, deliberately harmed himself in the past, and experienced a sense of hopelessness; and discharge was 'unplanned', important personnel were on leave/leaving, the consultant was 'new', admission was for less than a week, and the time lapse before contact was made with services after discharge was relatively long.

Feeney ea,(2005) looking at parasuicides seen in a Dublin general hospital emergency department, found that emergency staff had a tendency to overrate suicide risk relative to the evaluations of a liaison psychiatry service.

Prevention¹⁵³⁷ of CS

'Even with the best possible care, a small proportion of patients with major depressive disorder are likely to die by suicide'.(APA, 2002, p. 491)

'Suicide is not solely positioned in the domain of mental health services'.(Department of Health and Children, 2003)

'Since suicide is affected by sociocultural factors, there is no safe indication that what has worked somewhere will work elsewhere'.(Bertolote, 2004)

'...the diversity of causes is so great as to ensure that any search for generic solutions is futile'.(Walsh, 2008, p. 59)

The psychiatrist should strive to develop and maintain a therapeutic relationship with the patient.

Frequency of consultations should reflect the results of suicide risk assessments¹⁵³⁸. However, extraneous factors may operate between appointments to undermine our best efforts.(Simon, 2008, p. 1648)

Documentation should be sufficiently robust to reflect the efforts of the treating clinician.

The least likely to telephone SANELINE in Britain are males and young people (Fakhoury, 2000) and whilst young men are over-represented in Irish suicide statistics they are unlikely as a group to use mental health services.(Burke & McKeon, 2007) Any attempt to reduce CS rates must take account of the complex

¹⁵³⁵ Not all cases involve mutual consent, e.g. the coerced female survivor with no history of mental illness or self harm and the dead, depressed, male instigator who had a history of self harm.

¹⁵³⁶ Although the term is also sometimes used to cover suicide pacts.

¹⁵³⁷ Under the *Health (Miscellaneous Provisions) Act 2001* the Irish Minister for of Health and Children reports each year to both Houses of the Oireachtas (legislature) on measures taken by health boards during the previous year to prevent suicide, basing his/her report on the Annual Report of the National Suicide Review Group. The Health Services Executive published a strategy for suicide prevention in 2005 (Health Services Executive, National Suicide Review Group, and Department of Health and Children, 2005) which acknowledged that no one group can take on this preventive role on its own.

¹⁵³⁸ Risk assessment is particularly important at the time of discharge.

array of forces acting together to produce these rates. Also CS rates may not be a good indicator of mental health service delivery.(Desai ea, 2005) Calling things by different names, such as ‘unnatural deaths’, tends to blur official suicide rates. Restriction or removal of one method may be replaced by another,(Ohberg ea, 1995; Isometsa & Lonnqvist, 1998) although efforts in this area (which must be monitored for compliance) are worthwhile. Certainly, a dramatic example of a measure that led to a reduction in CS is offered by the substitution of coal gas (carbon monoxide) by natural gas: Kreitman (1976) suggested that this led to a 30% fall in English CS rates but Walsh (2008, p. 62) is sceptical about any such effect in Ireland¹⁵³⁹. Car exhaust toxicity was reduced by legislation on catalytic converters. Nevertheless, determined people will most probably find a way to end their lives,(Edwards, 1995b) and car exhaust seems to have been replaced by hanging.(Amos ea, 2001)

Most suicides have avoided contact with mental health services, only some 25-30% having had contact annually with such services in the UK. However, contact with the GP in the month before death (often for physical complaints) may be more common (50%) in the elderly suicide.(Harwood, 2008, p. 559)

Native American Indians who kill themselves were less likely to attend health services than those who attempted suicide.(Gaw, 2001, p. 33)

Luoma ea,(2002) in a review of 40 studies, found that 3 of 4 and 1 of 3 CS cases had primary care and mental health service contact respectively within a year of death; 45% and 20% had primary care and mental health service contact respectively within a month of death; and older adults were more likely than younger adults to see their primary care provider within their last month of life. In a retrospective study relying on accident and emergency records, 39% (85) of 219 ‘probable’ CSs in Leeds attended an accident and emergency department in the year before death, but only 15% of these were because of non-fatal self-harm; final visits occurred a median of 38 days before demise.(Gairin ea, 2003) According to Carroll-Ghosh ea,(2003, p. 1474) over three-quarters of patients seen by health care professionals within a month of CS ‘do not communicate their intent to do so’.

Cohen (2003, p. 438) points out that 10-40% of eventual suicides make prior attempts on their lives, 60-90% of suicides do not make prior attempts on their lives, and, therefore, if we were able to prevent everyone who had made prior attempts on their lives from killing themselves we would still not prevent the majority of suicides!

We do not know how many ‘parasuicides end up in Heaven’ by accident and how many ‘parasuicides’ are actually failed suicides. Bostwick and Pankratz (2000) reported an 8.6% lifetime prevalence of CS in those who were ever hospitalised for suicidality; among affective disorder patients who were hospitalised without specification of suicidality the lifetime risk of CS was 4%. It is far from clear what psychosocial and physical interventions prevent repetition of self harm.(Hawton ea, 1998) Van der Sande ea (1997) compared an intensive psycho-social intervention (brief admission to special crisis unit and problem-solving after care) with whatever care the clinician thought appropriate and found no differences in outcome on a number of measures such as repeat of AS or hopelessness scale scores. Increases in admission after overdose of psychotropics have paralleled increases in admission after overdose of non-prescription analgesics, suggesting a trend that may be outside medical power to change. Economic and social policies (jobs, social cohesion, etc) are more likely to affect CS rates than would medical or public health measures.(Kelleher, 1998; Appleby ea, 1999; O’Shea ea, 2000; De Leo, 2004) However, some social findings in CS might derive from psychopathology and alcohol abuse. A programme aimed at removing stigma from help-seeking, improving knowledge of mental health issues, increasing coping skills, and changing policies and social norms in the US Air Force is reported to have produced a sustained reduction in the CS rate.(Knox ea, 2003) Programmes aimed at school children have been shown to be effective.(Walsh, 2008, p. 62) Rising rates of CS in children and adolescents must ultimately point to psychosocial stress. Reductions in socioeconomic deprivation may reduce suicide rates, especially in young men.(Hawton ea, 2001b) Chiles and Strosahl (2005, p. 191) believe that we resort too readily to hospitalisation for suicidal behaviour. It may inadvertently reinforce such behaviour. Doctors should focus on treating mental illness. People should be encouraged to see their doctor and to say how they feel. The doctor should be vigilant and forthright in questioning about thoughts of self-harm. Enquiries should be made about any plans and preparations relating to suicide. Monitoring of compliance needs to be improved, especially in males and young people. A documented pre-discharge suicide risk evaluation is a wise

¹⁵³⁹ ‘As always there were other methods [of committing suicide]’. (Walsh, 2008, p. 62)

practice. Improved ward design and removal of fixtures that can be used for hanging are common-sense approaches to reducing suicide among in-patients.(Meehan ea, 2006)

Interventions that might protect the patient in hospital¹⁵⁴⁰ (Hunt & Kapur, 2007)

Be particularly vigilant during first week
 Review structure/layout of ward
 Remove potential ligature points
 Keep observation protocols under review
 Exits from open wards should be observed carefully
 Consider supervision for patients on leave

Interventions that might protect the patient after discharge (Crawford, 2004)

Periods of trial home leave before final discharge
 Information about problems that may be experienced at home
 Advice on sources of support and help
 Avail of experience of other service users
 Nurses that help patient regarding health services/carers/follow-up/crisis
 Meeting with out-patient staff
 Buddy system involving trained service users
 Day hospital attendance
 Early out-patient follow up¹⁵⁴¹

Interventions that might protect the patient in prison (Dooley, 1997; Frater, 2008)

Improved monitoring, especially at time of reception and young people
 Attention to substance use and mental illness
 Safer cells
 Remove ligature points
 Better access to meaningful activity/Samaritans/trained listeners
 Post-release arrangements for support

Research performed in Dublin (Bolger ea, 2004) suggests that young people want to talk to someone when in crisis; they asked for access to an informal, 24-hour service provided by staff with experience in mental health, alcohol and substance disorders. Hunt ea (2006) stress targeting schizophrenia, dual diagnosis and loss of service contact in young people. Particular attention should be paid to detecting and treating depression in the elderly, especially those who have a physical disorder or who are socially isolated.(O'Connell ea, 2004; Hunt ea, 2006)

The vexed question of what to do about the intoxicated person who expresses suicidal thinking was addressed by McCaffery ea.(2002) They found no specific guidelines from the RCPsych and little consensus among psychiatrists. Not surprisingly, the Medical Defence Union's opinion was couched in terms of terms of self-defence for a possible future legal hearing. Walsh (2008) stated that reducing alcohol consumption would reduce CS rates but bemoaned the fact that little had been done about this at a national level. Indeed, the monies necessary to fund official tackling of suicide in Ireland have been slow to materialise.(Mulholland, 2009)

Education of GPs on suicide and depression produced useful short-term reductions in CS rates in one famous study (Gotland), but it was estimated that booster courses every few years would be needed to maintain the effect.(Rutz ea, 1992; Morris ea, 2005) According to Baldwin ea,(2002, p.102) until more definite evidence becomes available, the most useful strategy in reducing suicide rates in the elderly is the diagnosis and management of depression by GPs.

In real life, treatment of depression with antidepressants reduces the risk of suicide in all age groups¹⁵⁴².(Cougard ea, 2009) Rising unemployment rates are associated with increases in rates of suicide,

¹⁵⁴⁰ Fawcett ea (2003) reviewed CS of 76 inpatients: 42 were on 15-minute observations and 9% were being 'specialled' (1:1 nursing) or with a member of staff at the time of death!

¹⁵⁴¹ See also Meehan ea.(2006)

¹⁵⁴² This study, a decision analysis model, compared depressives given antidepressants versus those not given these medicines. Sensitivity analysis showed that continuing to take the medication was the most important preventative measure.

homicides, and deaths from alcohol abuse, and, not surprisingly considering the cost of fuel, a decrease in road-traffic deaths.(Stuckler ea, 2009)

Self-mutilation/self-cutters (non-suicidal self-injury)

The commonest methods of self-injury in one British study of attendees at an accident and emergency department (Horrocks ea, 2003) were self-laceration (72.4%), punching walls/banging head (8.6%), and hanging (4.7%). In contrast to self-poisoners, wrist-cutters are classically younger, commit acts of low lethality, are no more likely to have made previous suicide attempts, complain less of depression but more frequently of feeling empty or tense, have sudden unpredictable mood swings, are often diagnosed as having a personality disorder, are abusers of drugs and alcohol, experienced sexual difficulties and are promiscuous, came from broken homes with parental deprivation, have difficulties in communicating, and leave hospital against medical advice. The typical pattern involves painless cutting after a period of depersonalisation, followed by relaxation and repersonalisation after bleeding. Some feel better after seeing their own blood.

Hawton and Catalan (1987) classified self-injury (other than overdose) into superficial self-cutting (usually wrist or forearm - little or no association with suicidal intent), serious self-injury (e.g. deep cutting, shooting, hanging, jumping from a height - usually associated with serious suicidal intent), and self-mutilation (these patients may be disfigured, are usually psychotic, and may or may not endanger life).

Van der Kolk ea (1991) found that cutters had a history of childhood trauma, neglect and abandonment. Such patients may react to life stresses as a return to earlier experiences. Dissociation under stress is not uncommon.

Tantam and Whittaker (1992) urge viewing self-wounding as a communication ('to influence the behaviour of others and to manage internal emotions': Lloyd-Richardson ea, 2007); the therapist should assist the patient to express need more adaptively. The positive side of suicidal ambivalence needs reinforcement.(Chiles & Strosahl, 2005, p. 28) Cognitive and behavioural techniques may help.

In most cases, self-inflicted injury is only part of a long history of psychogenic illness. The family is often very disturbed and may harbour a 'secret' such as sexual abuse. Life circumstances may play an important part in determining whether remissions occur in the future. In general, the main associations with self-injury are intellectual disability, psychosis, being in prison, and having a disorder of personality.

Self-mutilation is common among soldiers in battle. This may be a ploy to get home, the British 'Blighty wound'.

Joyce ea (2010) conducted a family study on the molecular genetics of depression and personality in which a proband had been treated for depression. They concluded that self-mutilation and attempted suicide overlapped only partially although both phenomena could be predicted by mood disorder diagnosis and harm avoidance. They found that self-mutilation had a strong association with bipolar affective disorder and they urged readers to consider the latter rather than borderline personality disorder when assessing self-mutilation. It seems to this author that one should consider both conditions in practice and these findings (Joyce ea, 2010) will need further research to see if they apply more generally to self-mutilators.

Morbidity in the Medical Profession

'More than ever before, clinicians are being asked to do more with less and treat complex disorders in time-limited fashion'.(Rudd, 2000)

'Management must be more accountable for the doctors in its employment'.(Murphy, 2005)

'At the organisational level, physician burnout is associated with reduced workplace productivity and efficiency'.(Wallace ea, 2009)

A survey of US doctors in the early 1990s found that 40% would not choose the same career if they were starting all over again. Research on stress in the medical profession is strongly associated with Firth-Cozens, a clinical psychologist in Leeds. Firth-Cozens (1994, 2003) points out that work stress originates from a complex interaction of doctor (self-critical, blame-accepting), work environment (lack of support, unreasonable demands), poor education (time management, ways of dealing with difficult patients¹⁵⁴³) and

¹⁵⁴³ See Lalanda (2009) for a discussion of dealing with the 'challenging patient'.

so on. It has been argued that doctors may enter medicine because of some early noxious life experiences and that, when medicine fails to help them resolve such conflicts, they become disillusioned and distressed. According to Firth-Cozens,(2003) 28% of doctors and 18% of the general working population suffer from excessive stress levels. Stressed doctors err more often. Predictors of a more positive work milieu include high self esteem, satisfactory support with work-related problems, lower perceived workload, a positive view of leadership, low work-related exhaustion, and having a sense of participation in the organisation.(Thomsen ea, 1998)

Factors leading to low morale and caseness on GHQ-12 in the medical profession (Thompson, 1988)

High work demands/insufficient resources

Role ambiguity – responsibility without authority; multi-professional team members 'equal'

Role conflict – loyalty to employer v loyalty to patient

Poor social support – less support from colleagues in the community than in hospital ('staff mess')

Lack of feedback on job performance – e.g. How am I doing? How do I develop personally? Longterm career plans?

Lack of influence on workplace decisions – managers plan and consultant input negated

Compromising professional standards – inability to tailor interventions to individual patients – possibly related to catchment area/sectorisation

Mental illness is common in doctors, especially alcoholism, drug dependence, and affective disorders. It may be the characteristics of the empathic doctor that make him prone to breakdown. Sources of stress include diagnostics and therapeutics, the death of children, domestic problems due to work, premorbid factors including personality variables, job insecurity, frequent moves, poor intercollegiate relations, demanding relatives of patients, administrators, being asked to be administrators instead of clinicians,(Stranjalis, 1993) rapid changes in job structure, long hours, over involvement with patients, and living in unfamiliar cultures. Perceived stressfulness is equated with 'overwork', but this is not necessarily directly related to the number of hours worked (Murphy, 2009)¹⁵⁴⁴; it is also equated with 'talking to distressed relatives', 'effects on your personal life', and 'serious treatment failures'.(Firth-Cozens, 1987) Sleep deprivation and fatigue probably has a greater adverse effect on routine duties than on emergency responses or novel situations.(Samkoff & Jacques, 1991) Quality of sleep (e.g. expecting to be called) may be important. However, reports of juniors falling asleep when driving are very worrying.(Marcus & Loughlin, 1996) Lack of sleep may impair performance and lead to symptoms of depression, anxiety, confusion, anger, and psychomotor impairment.(Gaba & Howard, 2002) Concern has been expressed about the implications for patient safety and quality of care provided by overworked doctors in America, as well as the resultant mental health of such physicians, senior as well as resident (i.e. housemen).(Gaba & Howard, 2002) US paediatric residents who are depressed¹⁵⁴⁵, but not those who have burnout, make an excess of medication errors.(Fahrenkopf ea, 2008) West ea (2009) found that fatigue, sleepiness, burnout, depression, and reduced quality of life were independently associated with an increased risk of future self-perceived medical errors among Mayo Clinic residents. Doctors in Jerusalem who have PTSD have excess anxiety, depression, negative coping strategies, and burnout, and are reluctant to receive treatment.(Einav ea, 2008) American doctors are more likely to be divorced if they are psychiatrists (surgeons come next), female, married before graduating, have low academic achievement, if the parents do not die before the doctor graduates, if they have high anger levels or perceive themselves as being less emotionally close to patients.(Rollman ea, 1997)

Mental health of psychiatrists (Firth-Cozens, 2007)

High levels of depression, burnout¹⁵⁴⁶, stress, and suicide¹⁵⁴⁷

¹⁵⁴⁴ Although it is often subjectively put down to long hours and, in England the Court of Appeal decided in 1991 that health authorities must not injure a doctor by requiring excessive hours of service.

¹⁵⁴⁵ 20% and 74% of the sample met criteria for depression and burnout respectively. This was a small, brief study with a 50% response rate and a low number of errors. Selection bias cannot be ruled out.(McLay & Ross, 2008)

¹⁵⁴⁶ See Harrison.(2007)

Low job satisfaction

Possible increased rate of alcohol/substance misuse¹⁵⁴⁸

Sexual relationships with patients (boundary violations)

Causes: organisational (clinical/administrative load), individual vulnerability (e.g. early experience of abuse, family history of psychiatric disorder)

Doctors have an excess mortality from suicide, hepatic cirrhosis or accidental poisoning. The higher rate of suicide among doctors may partly be explained by more successful attempts at suicide. 85% of female doctors have children within a decade of qualifying, which often leads to a conflict between family and career. Female doctors may be more inclined to early suicide than are male doctors. Also, according to the British Medical Association, (BMA, 1993) perhaps half of female junior doctors become depressed. Young male doctors are the most likely medical practitioners to be assaulted, especially if they are in psychiatry, and particularly if they are in training as psychotherapists. (Davies, 2001; O'Shea, 1988; Dhumad ea, 2007¹⁵⁴⁹; Rush ea, 2008¹⁵⁵⁰) In the UK, psychiatrists, accident and emergency doctors and GPs are the most vulnerable to violent attack (Schnieden, 1993) whereas women doctors and doctors in radiology, pathology, psychiatry,¹⁵⁵¹ and anaesthesiology may be at particularly high risk of suicide. (BMA, 1993) High levels of

Like Chiron (half-man, half-injured beast) of old, doctors are sometimes viewed as being better healers if they have experienced personal suffering. The idea that doctors must show persistence, ability to delay gratification, love of hard work and self-sacrifice, and an unwillingness to express career doubts can be dangerous. Job stress increases as the demands of work increase and decreases with increased feelings of control over the job and improvements of social support. People like to feel they are being rewarded for what they put into their job.

Kumar (2007) suggested that burnout is particularly common among psychiatrists, which is debatable. The argument is that psychiatry is a stigmatised branch of Medicine, that psychiatrists are always struggling for resources, and that complex judgments are part of the job.

Lucey (2009) has reviewed the concept of burnout, a phenomenon that is not unique to Medicine but one that afflicts about one-fifth of doctors. Leaving out people who are totally unsuited to the practice of Medicine, work overload, feeling poorly managed or poorly resourced, direct involvement in the suffering of others, high patient expectation levels, home-work interference, domestic interruptions, administrative load, and personal characteristics (committed, high-functioning, external locus of control, avoidant, obsessional/perfectionist, a tendency to feel rather than think, low stress tolerance, and low self esteem) are risk factors. Working for an organisation that appears to lack values or is cynical is unhelpful, as is lone practice. Victims complain of physical and emotional exhaustion, diminished personal accomplishments in previously high-functioning individuals, cynicism, and reduced ability to care. There are irritability, problematic absenteeism, and reduced job satisfaction. All aspects of life, including domestic, are adversely affected. It is not due to another mental disorder.

Solutions to burnout must come from multiple sources, e.g. the employer, clinicians themselves, colleges, and society. It would be very interesting to study the reasons for 'early retirement', even when it is a contractual option. Practitioners should feel able to acknowledge that the problem exists. Many issues need to be addressed, such as sense of control over work, part-time work/flexi-time, child-care, holiday leave/cross-cover/locums, career breaks/change, sabbaticals, and modulation of the workplace/home interface. Other important matters to be addressed are building a vision and trust in the mission, reasonable rewards, fairness, and consistency. (Lucey, 2009) Counselling for burnout in Norwegian doctors reduced emotional exhaustion and less exhaustion was associated with working less hours. (Isaksson Rø ea, 2008)

¹⁵⁴⁷ According to Thapar (1989), it has not been confirmed by research that psychiatrists are particularly prone to suicide within the profession.

¹⁵⁴⁸ US medical students who drink excessively may be less likely to see the point in counselling patients about alcohol. (Frank ea, 2008b) It is the author's experience that this fact applies more generally within the medical profession.

¹⁵⁴⁹ Dhumad ea (2007) found that London psychiatrists (64.8% response rate) were most vulnerable to assault if junior (32.4% over 12 months for SHOs v 12.4% of all psychiatrists) or on a psychiatric ward, there was little or no formal psychological help, and vulnerability was not influenced by prevention/management of violence courses or by attitudes to violence on the part of their patients.

¹⁵⁵⁰ This questionnaire study of psychiatric trainees in Ireland suffers from having only a 46.5% response rate. Training in breakaway and induction seemed good but 72% felt threatened and 16% had been physically assaulted.

¹⁵⁵¹ Famous names include Socrates, psychoanalysts Wilhelm Stekel and Bruno Bettelheim, artist Vincent Van Gogh of Holland, and psychiatrists Frank Fish of Liverpool and Richard Asher of London. Ludwig II of Bavaria drowned both himself and his psychiatrist (Bernhard von Gudden, inventor of the microtome) in Starnberg Lake in 1886! The Englishman, Thomas Addison (1793-1860), of anaemia and adrenal fame, suffered from severe bouts of depression and ended his life by jumping from a window in Brighton. The Alsatian Joseph Meister (1876-1940) who was vaccinated against rabies in 1885 by Louis Pasteur became concierge of the Institut Pasteur and shot himself when he failed to stop Germans from entering the crypt where Pasteur's body lay. Ernest Hemingway and a number of his relatives were victims of suicide. Some other examples are given in the table:

Name	Year of death	Detail	Method
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stress, anxiety and depression have been found among senior doctors and managers in the British National Health Service. (Caplan, 1994) Richards (1989) reported that over three-quarters of doctors surveyed had treated themselves with antibiotics, a quarter with hypnotics, almost one in twenty with antidepressants, and almost 3% with opiate analgesics. Availability and knowledge of pharmacology and therapeutics are important factors in suicide within the medical profession.

Anxiety is a common complaint among doctors. Extra stresses on female doctors include lack of senior female role models, conflicts between career and family, prejudice and attitudes of male colleagues, and loneliness. Litigation is a major modern stressor.

Working in ICUs carries particular stresses. Accident and emergency departments carry certain stresses for juniors: intense workload, diagnostic uncertainty, unsociable hours, and fatigue.

15-35% of medical students suffer from some form of psychiatric morbidity. Perceived sources of stress include consultants (!), exams, finances, and family issues. Some are afraid to seek advice in case this might have adverse career implications. (Gaughran et al., 1997) Curran et al. (2009) used the BDI and the CAGE with medical and business students at TCD and UD in Dublin. The response rate was 62.7%. Almost 14% of students scored at least 10 on the BDI and a quarter scored at least 2 on the CAGE. The only difference between the two groups was that alcohol abuse was more common among business students than among medical students. About 6% of students reported suicidal thinking in the last month and such thinking was more likely in the presence of stressful life events and absence of social support.

In the first postgraduate year, one-quarter to one-third of interns suffer from clinical depression, but this figure tends to decline with the passage of time. Long hours, lack of sleep, poor diet, poor social supports, large bank loans, feelings of inadequacy, and separation from home may be important factors here, as are the abuse of alcohol, and the use of drugs for physical illness or for recreation. (Firth-Cozens, 1987) US interns (Sen et al., 2010) showed a significant increase in depression scores on the 9-item *Patient Health Questionnaire* during internship and this increase was associated with certain pre-internship (being female, US medical education, difficult early family environment, history of major depression, and increased neuroticism) and intra-internship (long hours of work, perceived medical mistakes, and stressful life events)

Antony, Mark	30 BC	Roman politician/general	Stabbing
Berger, Hans	1941	Invented EEG	Hanging
Brutus	42BC	Assassin of Julius Caesar	Stabbing
Capucine	1990	French actress	Jumping
Cleopatra	30 BC	Egyptian ruler	Snake bite
Clive, Robert	1774	Clive of India	Cut throat
Diesel, Rudolf	1913	Inventor of diesel engine	Drowning
Freud, Sigmund	1939	Father of psychoanalysis	Morphine
Gelhorn, Martha	1998	US war correspondent	Poison
Goebbels, Joseph	1945	Nazi propagandist	Poison
Hancock, Tony	1968	British comedian	Overdose
Hannibal	182BC	Of elephant fame	Poison
Hitler, Adolf	1945	Nazi dictator	Gunshot + cyanide
Iscariot, Judas	33 (?)	Sold Christ for silver	Hanging
Konoe, Prince Fumimaro	1945	Japanese war criminal	Cyanide
Krupp, Friedrich Alfred	1902	Industrialist/homosexual	Controversial (stroke?)
Levi, Primo	1987	Italian author	Jumping
Monroe, Marilyn	1962	US actress	Overdose (controversial)
Nero	68	Roman emperor	Stabbing
Plath, Sylvia	1963	US poet	Gas
Raubal, Geli	1931	Hitler's niece/lover	Controversial (murder?)
Ray, Margaret Mary	1998	David Letterman stalker	Locomotive
Rommel, Erwin	1944	German field marshal	Poison (to save his family)
Rudolf, Crown Prince	1889	Austro-Hungarian heir	Suicide pact (murder?)
Sanders, George	1972	British actor	Overdose
Spilsbury, Sir Bernard	1947	British forensic pathologist	Gas
Stevens, Inger	1970	Swedish actress	Overdose
Tone, Wolfe	1798	Irish patriot	Cutting
Vicious, Sid	1979	Of the Sex Pistols	Heroin
Wells, Horace	1848	Dentist, early anaesthetist	Cutting + chloroform
Woolf, Virginia	1941	British novelist	Drowning
Young, Gig	1978	US actor	Gunshot (murder-suicide)

factors; also, having at least one copy of a less-transcribed 5-HT transporter protein gene was associated with increased likelihood to report depressive symptoms during internship. When the *GHQ* and *Symptom Checklist for Depression* were used, 46% of one group of female junior doctors scored above the criterion for depression.(Firth-Cozens, 1990) Medical students may also show high levels of psychosocial morbidity. Creed(1993) reckoned that doctors' spouses have a standardised mortality ratio of 275! Junior doctors, especially if female or foreign, often perceive that they are subject to bullying.(Quine, 2002; Cheema ea, 2005)

General practitioners (GPs), who are prone to depression,(Caplan, 1994) experience stress from night calls, emergencies during surgery hours, and interruptions in family life. Violence against GPs is particularly likely during nocturnal home visits. Anxiety, intoxication, and long waits are important precipitants.

Relatives may often be the aggressors. Training in coping strategies and time management may benefit GPs,(O'Sullivan ea, 2005) as it would other members of the profession.

Thapar (1989) points out that prevention and early detection are important. Support groups ('three wise men', 'sick doctor schemes', etc.¹⁵⁵²), guaranteed confidentiality, and brief psychotherapy can all play their part, and university psychiatric help for students should be widely available. Doctors should not be made to feel stigmatised if they seek help, and treatment should not be unduly modified because of their professional status. Senior staff should take an interest in their junior and be supportive. Doctors have to overcome stigma, misguided professional loyalty, a tradition of self-treatment, and fear of jeopardising career and job prospects if they are to step forward for help. Female doctors should never be discriminated against. Doctors should not hope that drug dependent colleagues will somehow snap out of it, making this a excuse for inactivity. Experience in the US suggests a favourable outcome at five years for physicians treated for substance use disorders and that the programmes offered have an appropriate mix of therapy, support and sanctions.(McLellan ea, 2008) Similar positive outcomes have been recorded in Canada.(Brewster ea, 2008) Rostering flexibility for working mothers and the needs of female staff need to be taken into account in planning.(Blunt, 1990) Shift systems may be superior to orthodox working schedules in selected instances. Doctors who give the impression of rushing an interview are more likely to be the objects of litigation or complaints about care. Not everyone understands that sometimes doctors are in a hurry.

Counselling or cognitive therapy may help stressed doctors. Part-time work is becoming more popular, as is early retirement. Seventy percent of British NHS psychiatric consultants opting for early retirement have cited bureaucracy and 52% interference by managers in clinical decisions.(Thompson, 1998) The actual workload needs urgent attention.(Benbow & Jolley, 1998) A safe working environment should be mandatory. To err is human and occasions of error should be tackled as learning opportunities,(Firth-Cozens(2003) although the litigiousness of society may militate against this in practice.

Doctors and responsible others should utilise strategies that reduce the level of stress to which they are exposed (see box).

Things doctors might do to reduce personal stress (after Iversen ea, 2009)

Doctor-initiated

Find and use mentors

Take care of self (exercise etc)

Reflect on ones emotions/reactions

Challenge your own unhelpful beliefs

Spend time with non-work related others (e.g. friends)

Ring-fence time for other things (e.g. religion, hobbies)

Time management

Employer/educator-initiated

Medical school – mentoring, peer support networks, training in team work and leadership, health care, asking for help

Junior medical years – supervision, discuss problem cases and mistakes, support network, work-occupation balance

Rest of career – flexible childcare, have say in way of working and workload

¹⁵⁵² Confidential 'phoneline for Irish Sick Doctor Scheme: 01-2887695. In Britain 'phone 0171-9355982 for local help.

Women: some further considerations

We may tend to place women on a pedestal, and deny her ability to be incestuous or otherwise a poor mother. (Wellson, 1991) Of women who kill, most kill their own offspring; of men who kill, only 3 in every 20 kill their children.

In the urban West, women with chronic severe psychiatric illness may be more likely to live with their families, while men live in hostels. (Conning & Rowland, 1991)

Depression in treated samples shows an approximately 2:1 female predominance. This applies equally to studies of prevalence in the community. According to Paykel (1991), much of the excess occurs in married women aged 25 to 45 years with children. Explanations might include expression of distress (depression in women, alcohol abuse in men), biology (hormones), and social (carer status, young children: see Kennedy & Hickey, 2005) factors. Romans ea (1993) conducted a follow up of New Zealand women in the community and found that onset of non-psychotic psychiatric disorder was associated with being separated or divorced, coming from a large family, having poor social networks, living alone, having few social role responsibilities such as a paid job or motherhood, being in poor physical health, and being financially insecure. Those women who were less likely to have their disorder remit were middle-aged, financially poor, and had poor social relationships at initial assessment. Psychosocial factors may be less important in determining outcome in severely depressed women. (Andrew ea, 1993) Premenstrual exacerbation of major depression is endorsed by by most female sufferers and it may be a marker for more prolonged episodes. (Kornstein ea, 2005)

Ashton (1991) reported that European and North American women are prescribed over twice as many psychotropic drugs as men.

Classical patient with thick-case notes (O'Shea & Falvey, 1991)

Female

Many admissions

Long periods in hospital

Presents early in life

Separated or single

Loses work during her illness

Excess of medical disorders

Reared in care, having lost a parent, in particular her mother, in early life

History of legal and social worker contact

Unstable psychiatric diagnosis

Often has a personality disorder

May have a low IQ

History of alcohol and substance abuse

Subjectively and objectively, the strain and burden may be greater in female carers of demented than in their male counterparts, perhaps relating to different role expectations and coping strategies. (Morris ea, 1991)

In 1991 (Oppenheimer, 1991), women comprised one-third and 1% of alcohol abusers in the US and UK respectively. Such abusers tend to be of childbearing age.

Women commit all types of crime but much less often than men. (Heidensohn, 1991) Female crime is often associated with socio-economic marginalisation. Courts may view women as doubly deviant. Provisions, in or out of custody, are inadequate for females. Women, as potential victims of crime, are more fearful than men are.

More women report a history of sexual contact in childhood (CSA) than do men. (Sheldrick, 1991)

Female referrals to an eating disorder clinic had a 30% history of CSA and a 52% history of having a personality disorder. (McClelland ea, 1991) Perkins and Rowland (1991) suggested that long-term community psychiatric services might not serve the needs of women as adequately as those of men.

Useful address

'Aware', 72 Lower Leeson Street, Dublin 2. Started 1985 by patients' relatives and mental health professionals to help tackle depression in Ireland. Tel: 00 353 (0)1-890303302. www.aware.ie.

Schizophrenia Ireland and associated organisations' site promoting awareness/understanding of mental illness/suicide:
www.headline.ie.

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12

Grief, normal and abnormal¹⁵⁵³

Brian O'Shea

'A touch or a hug will often do more to facilitate grieving than any words'.(Parkes, 1998)

'Death is not only the great equalizer, it allows us to value life'.(Levine, 2000)

'Those who can die live freely'.(Karen Blixen in Out of Africa, quoted in Göttsche, 2002)

'Death is seen as a tragic failure rather than the necessary culmination of a good life'.(Taylor, 2002)

'Traditional Christians craved the good death; moderns seek the prolongation of pain-free life'.(Porter, 2004)

Reactions to stressful experiences can be normal, as in uncomplicated grief, or abnormal, as in abnormal grief, PTSD, acute stress reaction, or adjustment disorder. PTSD may complicate grief. There is no time cut-off for normal grief. As part of the ageing process, people discard the youthful fantasies of immortality with varying degrees of success.

Definitions

Bereavement refers to the situation of having lost a significant other through death.

Mourning is the process of adjusting to bereavement.

Grief is the personal experience of mourning.

We can grieve for anything that we have lost,(Hollins, 2005) including friends¹⁵⁵⁴, pet animals, a limb, youth, physical prowess, or a famous person. Going into an institution such as a nursing home can be a major loss event¹⁵⁵⁵. We can grieve before we lose something, anticipatory grief. Mental illness in a close relative may evoke complex emotional reactions, including grief, hate, sorrow and fear of developing the same disorder.(Stålberg ea, 2004) Those given a chance to talk about a loss before it happens are often less distressed later than those not given the opportunity. Caplan, of crisis theory fame, elaborated on such primary prevention measures as the use of domestic pets to offset loneliness. Milner(1966) described a man with amnesia following bilateral temporal lobectomy that mourned afresh every time he learned that his uncle had died! Enlargement of the left ventricle has been reported in the bereaved. The support offered by a spouse may have a protective role for physical health during parental bereavement. Lack of social support, mental illness, conflict or excessive dependency, and alcoholism, may increase mortality after loss of a close other. Bereavement has early and late effects on mortality. It affects many aspects of a person's life. The early effects include coronary heart disease. Possibly, the earliest manifestation may result from ventricular arrhythmias. The last effects are less clear. It is difficult to distinguish the effects of social isolation and low social support on the heart from that exercised by bereavement, since men return to the

¹⁵⁵³ Modern scientific interest in bereavement dates to Erich Lindemann and the Coconut Grove fire in Boston, Massachusetts during World War Two. Lindemann influenced a generation of Boston investigators, including Gerald Caplan, Robert Weiss, and Colin Murray Parkes, Parkes bringing this work in England.(O'Shea ea, 1982) The British organisation 'Cruse - Bereavement Care', formerly the 'National Organisation for Widows, Widowers and their children', was founded in 1959 and offers counselling, advice, practical information, and opportunities for social contact. It is available to all those bereaved by death. Useful sources of practical information and contact numbers in Ireland are O'Connor ea (undated) and the *Irish Medical Directory*.

¹⁵⁵⁴ Loss of friends from AIDS has a deleterious effect on AIDS progression, even with HAART.(Leserman ea, 2007)

¹⁵⁵⁵ Prior vulnerability, contrasts between former and new living quarters, and the amount of say the person has in the move influence psychological outcome.(Tobin & Liebermann, 1976)

mortality curve of the control group once they remarry. Lymphocytic response seems to be diminished¹⁵⁵⁶ in early bereavement, in major depression and in other forms of stress, (Rogers & Reich, 1988) but enhanced immune response has been reported in those people anticipating grief. (Spurrell & Creed, 1993) Elderly widowers may be more likely to die in the months after loss of a spouse than are widows, (Benjamin, 1985) and widows have increased rates of both major depression and anxiety disorder during this time. (Surtees, 1995) However, it has been suggested that widows do better than still married women in the longer term because they have an increased sense of mastery and have learned new skills! The dying may displace their hostility onto the doctor and the aged may displace it onto the young who misspend their youth. Depression should be considered if the dying do not want to see relatives. Depression is common after the loss of a spouse, especially for young widows and widowers with a history of depression. (Zisook & Shuchter, 1991)

Doctors can feel disappointed because they don't achieve their own expectations. A patient's death may trigger personal fears or ideas of guilt in the physician. We need to grieve. A balance must be struck between ones own needs and those of our charges, we must acknowledge fallibility and accept help as needed. We too often see death as something to be avoided, postponed or resisted at the expense of a humanistic approach to the dying. (Clark, 2002; O'Shea, 2002; Cassem & Brendel, 2004)

Most people want to die at home whereas, at least in the UK, most will die in hospital, care home, hospice, or elsewhere. Only 18% die in their own homes in the UK. (Riley, 2008) Few people discuss how they would like to die.

Irish Medical Council 2009 guidance on end of life care (medicalcouncil.ie)

There is no obligation to start or continue a treatment or artificial nutrition and hydration that is futile or disproportionately burdensome, even if it prolongs life

The clinician should carefully consider when to start or stop attempts to prolong life but should ensure pain relief and reduction of distress

Patients may refuse treatment and clinicians should respect 'living wills' (advance healthcare plans)

If death occurs, discuss the circumstances with the family (unless patient recorded an objection)

Do not participate in any way in active killing of the patient

Gündel et al (2003) showed eight bereaved females photographs of the deceased and of strangers and they were also exposed to words specific to the death event and neutral words. Both stimuli (fMRI) activated the posterior cingulate cortex, the medial/superior frontal gyrus, and the cerebellum; the pictures activated cuneus, superior lingual gyrus, insula, dorsal anterior cingulate cortex, inferior temporal gyrus, and fusiform gyrus; whereas words activated precuneus, precentral gyrus, midbrain, and cerebellar vermis.

Distinguishing grief from depression*

Grief

Intense symptoms for at least 1-2 months**

Usually no suicidal ideation***

Visions or voice of deceased transient only****

Pangs interspersed with normal feelings

May blame deceased

Improves with time

*If in doubt, treat for depression – antidepressants do not retard the grieving process. See Kendler et al (2008) who doesn't see the value of distinguishing these two phenomena.

**Cultures differ in the degree to which distress is expressed openly, a fact that must be considered before labelling grief as being pathological. (Parkes, 2000)

***But bereavement was the commonest recent major event in the lives of Cork suicides for both sexes in Kelleher et al (2000)

****Often drowsy at the time of experience.

Depression

Longer duration

Such ideas are common

May have sustained depressive delusions

Continuous, pervasive depressed mood

Blames self

No change or worsening

With regard to stillbirth, it is important to know when to promote grieving and when not to blow the event up out of proportion in the mind of the bereaved. (Bourne & Lewis, 1991; Stillbirth and Neonatal Death

¹⁵⁵⁶ But mildly so. (Calabrese et al, 1987)

Society¹⁵⁵⁷, 1991) Not every woman wants to hold her stillborn child and not everyone who does fares better emotionally than those who never see the dead baby.(Hughes ea, 2002) Loss of a pregnancy may be associated with stronger grief reactions in women who lose the baby later in pregnancy, have a more neurotic personality, have more pre-loss psychiatric symptoms, and have no living children.(Janssen ea, 1997) Many women who lose a pregnancy will have symptoms of depression, anxiety and somatisation during the first 6 months or so, but are generally indistinguishable from women having a live baby at one year.(Janssen ea, 1996) The final chance of having a child by a relatively elderly couple that ends in a stillborn baby may be of vastly greater significance than an early spontaneous abortion affecting a young couple. Religion may offer solace for many,(Parkes ea, 2000, p.15) Therapists dealing with perinatal loss should suggest to relatives that they might consider keeping photographs and a footprint, registering a name and preparing a funeral. It is suggested that women experiencing a stillbirth be nursed on a gynaecology ward instead of a postnatal ward after delivery. Anticipatory guidance involves covering such topics as how to explain the loss to others, giving away clothes and toys, meeting friends with young babies, and anything else that may help the woman to cope when she goes home.

Fathers may be almost as anxious antenatally as the mother when there is a history of previous stillbirth.(Turton ea, 2006)

The death of a child may lead to depression and anxiety in the parents that take years to subside.(Kreicbergs ea, 2004a) Parents who feel that their child is aware that he or she is close to death may later regret not having talked about this to the child.(Kreicbergs ea, 2004b) The death of a child may be handled insensitively by professionals,(Finlay & Dallimore, 1991) and parents should have a say as to the setting wherein their child spends his/her last days, e.g. ICU versus a more homely ward.(Anonymous, 2007) Relatives need relatively unrestricted time with the body in a calm environment. Tokens of remembrance, such as hair or nail clippings, may be collected. Organ donation should be discussed in a very sensitive manner. It has been suggested that induction of delivery should be considered as soon as feasible after diagnosis of death in utero.

In the 'replacement child syndrome'(Cain & Cain, 1964) a child is specifically conceived to replace a dead sibling, or an existing sibling may be forced into taking this role. Such parents have an intense narcissistic investment in the dead child. The mother may have experienced unusually high numbers of family losses in her own childhood. The home may have a funereal atmosphere with a palpable obsession with links to the deceased.(Oglethorpe, 1989) Interestingly, Turton ea (2001) found that PTSD was common after stillbirth, especially if conception occurs soon after the loss.

Men may be more secretive about infertility than are women and men may experience difficulty performing sexually according to prescribed schedules. Occasional cases of infertility are associated with non-consummation or anorexia nervosa. The woman may feel empty, worthless or 'not like a woman'. She may harbour guilt over past sexual acts and regret over past induced abortion or she may blame herself for delaying attempts to conceive for career reasons. She may either increase or reject sexual activity. In some cases in vitro fertilisation (IVF) may simply postpone acceptance and grief work. Some cases who do conceive may paradoxically become depressed, possibly as a let down after years of fantasising about how wonderful ordinary parenting would be. Some couples may proceed to IVF too early because of advertising pressures.(Burt & Hendrick, 2005, p. 122) The artificiality of providing specimens and seeing doctors may interfere with the spontaneity of sexual (and other interpersonal) relations. GnRH agonists (e.g. leuprolide and goserelin), used for endometriosis, may cause depression or labile emotions. Clomiphene, used to induce ovulation, may be associated with depression, anxiety, and poor sleep. Assisted reproduction is associated with a small increase in low birth weight and congenital defects, although the great majority of such babies are normal. Older women who conceive as a result of medical intervention are at increased risk of having babies with chromosomal abnormalities. Support groups may help infertile couples.(Stotland, 1996)

When parents discover that their child is intellectually disabled they are less likely to reject the child if the latter is not grossly disfigured and if they have had time during which they can bond before a suspicion that not all is well can arise. They may develop grief because of lost hopes,¹⁵⁵⁸ anger that it happened to them or because they were wrongly reassured, denial of the reality of the situation, anxiety for future children or

¹⁵⁵⁷ Founded in 1978 in Britain as the Stillbirth Association.

¹⁵⁵⁸ Loss of the 'perfect child' (Bicknell, 1983)

about the effects of the disability on the index child or older siblings, or they may feel guilt and a sense of recrimination as they look for possible causes. They need a chance to talk and adjust. Chronic psychosis in a child may trigger severe, prolonged grief in parents.

The intellectually disabled themselves may express grief in ways other than speech, such as insomnia, anorexia, searching, externally-directed aggression, a decline in intellectual or other skills, incontinence, or indifference. The fact that intellectually disabled people are living longer means that more of them experience the death of loved ones.

The relatives of suicides tend to be shocked, to search for an explanation, to find it difficult to share feelings, to feel guilty or stigmatised (often reinforced by the media and others: Harwood *et al.*, 2002; de Groot *et al.*, 2007), or to feel relief (if the relationship with the suicide was poor). There may be an increased mortality from suicide among the bereaved following suicide, although attribution of cause is difficult because, for example, there may be a shared tendency to affective disorder. The same difficulty applies to interpreting reports of a history of exposure to suicide attempts or threats by friends or relatives in the histories of suicide completers: shared cultural and genetic factors act as confounders. Therapists, who may themselves be severely distressed, (Hendin *et al.*, 2004) should initiate early contact with the bereaved family. (Hawton & Simkin, 2003) Peers may suffer traumatic grief (Melhem *et al.*, 2004) and peer support groups may be helpful in coping with suicide among friends. (Ness & Pfeffer, 1990; Robinson, 2005) Murder of a loved one may be followed by persistent fearfulness, anger toward the perpetrator, and intrusive repetitive images of the murder as imagined to have happened. (Rynearson, 1984) Rynearson (1995) found that only child sexual abuse and lack of religious faith were associated with seeking treatment after the murder of a family member; adults who seek treatment under such circumstances are highly reactive to all measures of trauma, grief, and death imagery.

War produces many psychiatric casualties, including prolonged grief in young widows of combatants whose bodies have never been seen. The combat zone militates against the normal expression of grief. Different cultures have their own customs in situations of grief. (Parkes *et al.*, 2000) Black (1987) examined the ways of three Indian groups: Hinduism (e.g. the family is in mourning until the thirteenth day after the cremation, when a special ceremony takes place), Sikhism (various religious items, e.g. brooch, must be left on the body), and Islam (Moslems mourn for three days after the funeral and visit the grave every Friday during the following forty days). The Sikhs do not mind if the body is touched by non-Sikhs but the other two groups do¹⁵⁵⁹. Modern life in the West often means that people live far from families of origin so that coping with loss may be a lonely psychological task.

Loss of sight leads to grief. Denial may hamper rehabilitation. The prognosis should be made clear.

Voluntary organisations should be involved and groups, if available, are useful. Deafness and aphasia are other losses. Relatives need a shoulder to lean on.

Common losses, which elicit grief reactions, include close relatives, friends, sexual partners, social status, self-esteem, and even parts or functions of the body. The loss may be only feared as in separation anxiety. Freud held that the bereaved regresses and incorporates the lost object. His benevolent feelings can then be smothered by sadism without hurting the loved one because only himself is assaulting him. The memory is rejected, incorporated into the ego by identification, and finally it is brought before the superego for condemnation. Depression is more likely to follow loss if the relationship with the deceased was largely negative. According to Klein, we can handle loss better if we succeeded in childhood in relating to others, especially mother, as a whole person and were accepting of mixed feelings of love and anger. Winnicott saw the internalised image of a reliable 'good enough' mother from childhood as providing a lasting source of inner strength and confidence that helped us negotiate loss.

Lieberman (1983) holds that morbid grief may develop and become life threatening if bereavement is concealed from a patient and not discussed soon after the loss.

The first stage of normal grief is numbness, the shock being too much. Disbelief and denial take over. The person is dazed, depersonalised and in 'another world'. After hours to weeks the initial shock subsides. Reality encroaches on consciousness and anxiety rises. Blame may be aimed at the self or projected onto ambulance men, doctors, or elsewhere. Anorexia, preoccupation, declines in efficiency and constant going over the past are the order of the day. Normally, with the aid of defence mechanisms, recovery takes place over some months. Anniversaries and other reminders may bring back sadness later. Factors, which suggest

¹⁵⁵⁹ Wear gloves if it is essential to touch such a body.

that a family will effectively resolve its grief, include cohesiveness in the absence of enmeshment, an ability to grapple with conflict, and adaptability. Factors associated with maladaptive grief in families include poor or unresponsive communication, disengagement and stifling of emotional expression, excessive guilt or anger, blaming or fighting with other members, inability to resolve normal daily family conflicts, inflexible roles, and persisting dependence on the lost person. In other words, anything that avoids, distorts, or prolongs grief augers badly for the future. (Kissane & Bloch, 1994)

Renvoize and Jain (1986) reviewed anniversary reactions. Of particular interest is the case of a woman who lactated as part of an anniversary reaction to the delivery of her stillborn child. The defences employed include: searching by the bereaved; denial of the loss; talking about the loss ad infinitum; intellectualisation (talks without facing the associated feelings); identification with the deceased (dressing or talking like him, identical symptoms to those suffered by the deceased, etc.); somatisation (physical complaints); litigation against caretakers or others; idealisation (lost person praised to an exaggerated degree); and mummification or preservation of dead body, a lock of hair, or objects belonging to the deceased¹⁵⁶⁰.

C Murray Parkes studied bereaved psychiatric patients and devised his famous division of bereavement reactions into grief and modified grief and non-specific reactions.

Grief and modified grief: typical or usual grief (see above) follows fairly predictable course over a period of months, culminating in a return of interest in the affairs of the world. Chronic grief is a magnified reaction spread over a long period of time, and the person may have guilt, self-blame, identification symptoms and/or aggressive or delinquent behavior. In the very young or very old, inhibited grief is manifested by symbolic expression. Delayed grief means that weeks/years pass before symptoms occur. In a 13 month follow up almost one in ten subjects showed chronic grief but none had delayed or absent grief. (Middleton ea, 1996)

Non-specific reactions: psychosomatic disorders (ulcerative colitis, asthma), neuroses (hypochondriasis, phobias, depersonalisation), depression or mania, and others, such as alcohol abuse.

Parkes subdivided abnormal grief into (1) unexpected grief follows a major loss which is unexpected and untimely¹⁵⁶¹; anxiety, shock and disbelief are common; the dead person seems to be in one's presence; self-blame and the need to remain faithful make it difficult to express grief fully and hence to make a fresh start; (2) ambivalent grief follows loss of relationships which have been punctuated by fights and mixed emotions; the bereaved feels relief at the loss - relaxed at first; later there is severe pining and despair; it may become chronic and contain marked elements of self-punishment; and (3) in chronic grief, full grieving begins early but doesn't seem to end. Dependent relationships are more likely to end this way. Parkes makes the point that it is not always the 'dependent' partner who ends up this way, i.e. different degrees of symbiosis may exist so that it is the apparently stronger, domineering partner who may lose out emotionally through loss of someone to smother.

The intellectually disabled respond to loss, often for the only person who understands them, with behavior or neurotic problems. They may be kept back from the funeral or placed in an institution with unfamiliar surroundings, often facing strangers for the first time, when their carers die. (McLoughlin, 1986) Whilst bereavement experienced by children may necessitate major readjustment, most of them develop normally after such an event (*vide infra*). Young and Papadatou (2000) state that children should be encouraged (but not pressured) to attend funerals, be supported by trusted elders, and be given an opportunity to see and touch the deceased.

When a young child is cared for by strangers in a foreign environment he often shows a classical sequence of responses: protest, despair, and then detachment. When the child returns home he shows clinging behavior because of separation anxiety.

Emotionally neglected children may show none of the normal fretting and so on when placed in hospital. They may eventually take an excessive interest in hospital staff¹⁵⁶²; autistic children, on the other hand, do not improve rapidly on removal from the home.

John Bowlby and others have undertaken detailed studies of the development of affectional bonds and the consequences of their disruption at the Tavistock Clinic. The Platt Committee's findings incorporated

¹⁵⁶⁰ Queen Victoria left out Prince Albert's breakfast tray after his death.

¹⁵⁶¹ Unexpected death of a loved one may precipitate PTSD. (Breslau ea, 1999) In fact, within the average community, sudden loss of a spouse may be a more frequent cause of PTSD than are the various forms of personal violence. (Breslau ea, 1998)

¹⁵⁶² Reactive attachment disorder in DSM-IV is divided into the wary child with frozen watchfulness and the over friendly one who indiscriminately goes to anyone.

recommendations based on their research. Mothers were not to find their children unavailable outside hospital visiting hours. The separation was most traumatic when the child was in his second or third years. James Robertson made the famous film 'A Two-year-old Goes to Hospital' in 1952. From this work developed a form of psychotherapy for anxiety, depression or emotional detachment. The steps are: provide a secure base for the patient; explore self and relationship with others; examine client's subjective views of on-going relationships, including that with the therapist; examine his deductions about relationships and the actions he takes as a result; ask if his reactions are appropriate; and ask why he reacts in these ways. Are his ideas based on unresolved and earlier attachment problems?

One of the things that a child learns growing up is constancy. An object torn into two pieces still has the same volume as the whole. If mother leaves the room she has not run away. Later on we know that if a boyfriend talks to another girl he has not necessarily decided to be unfaithful. Failure to incorporate these emotion-laden lessons is at the root of much adult morbid jealousy and separation anxiety.

Early loss of a parent is important. Parental loss before the age of 17 years has been said to increase the chances of depression developing in later life. (Browne *et al.*, 1977; Roy 1978) Roy (1981 a, b) has added further evidence for this in depressives and in chronic undifferentiated schizophrenics. The role of early parental loss in attempted suicide is still controversial. What may be more important is the reason for the loss - it may be unrelated if it occurs through natural causes - and it may be more related to parental discord and intentional separation of parent from child. (Crook & Raskin, 1975) Perris *et al.* (1986) do not support early loss of a parent through death as a precursor of adult depression, 'though parental death may be an important variable for individual patients'. Deprivation of love may be an important psychological risk factor in the background of depressive disorders.

Bereavement in the elderly is a life event with significant consequences for personal health. Some areas keep an at-risk register of the recently bereaved. Local resources, official and voluntary, are employed in crisis intervention to avert disaster, such as suicide.

An interesting problem is the case of the demented spouse who functions reasonably well before the death of the supervising partner, only to need institutional care immediately thereafter.

Brown, Birley and Paykel have done pioneering work on life events. It has been recognised for many years now that the mortality rate rises steeply among the bereaved during the first 6-12 months after bereavement. Coronary thrombosis occurs in excess during this period.

Brown postulated that the intermediate factor might be depressed affect:

LOSS → DEPRESSION → CORONARY THROMBOSIS.

Illnesses often cluster together. Rahe, in the 1960s, found that the death of a spouse was regarded as possibly the most stressful of life events. Bereavement may be associated with increased adrenocortical activity and increased serum prolactin and growth hormone levels.

There are many mundane factors at work in the bereaved, such as self-neglect, poverty, ambivalence towards the deceased, anxiety for one's own health, and lack of companionship. (see also McAvoy, 1986)

The widowed of both sexes have an increased mortality if they change their address. (Helsing *et al.*, 1986) Bereaved people need to balance confronting and avoiding loss in order not to be overwhelmed. Grief stages (numbness, pining, disorganisation/despair, and reorganisation) are not rigid and can pass back and forth.

Caplan urged that professional help be given early in social *crisis*, believing that the best work can be done in the initial 4-6 weeks, it being then that the patient is most open to influence. In the management of psychiatric breakdown in battle Sargant and Slater had been advocating early intervention since World War II. Erich Lindemann's (1900-74) study of the Coconut Grove nightclub fire¹⁵⁶³ (1944) underlies much of Caplan's crisis theory.

In the 1970s, Mechanic divided people experiencing stress into Copers and Non-Copers. People vary widely in the effect that stress has on them. Important determinants of this are previous experiences of stress and the circumstances prevailing at the time, presently available supports, affective state, and the symbolic significance of the event and its immediate antecedents for the individual. During the early 1940s, Adler examined 46 victims of the Coconut Grove disaster who were treated in a Boston hospital. He

¹⁵⁶³ Club in Boston, November 28, 1942; 491 fatalities.

diagnosed anxiety neurosis in 25 at three months and in 13 at nine months. There is little scientific evidence to support a contention that the Samaritans¹⁵⁶⁴ have any real effect in reducing the suicide figures, although they do provide a valuable service for the distressed and lonely. Also, there is evidence that contacting people by telephone one month after discharge from an emergency department for deliberate self-poisoning may help to decrease the number of repeat attempts over one year. (Vaiva et al., 2006)

Grief is a normal reaction to the loss of physical function. It is often misdiagnosed for major depressive illness. (Steward & Shields, 1985) The prognosis in such cases depends on the severity of the disability, the premorbid personality, and the available supports in the family, community, and so on. The symptoms of grief include preoccupation with the lost object (limb, function, person), physical distress, inappropriate behavior, hostility and denial. These signs weave in and out of the patient's daily activities, and wax and wane over the course of time. Amputation or loss of a body part can be particularly problematic in those who avoid facing up to the loss, are obsessed with it, or who have unresolved sexual problems. (Maguire & Parkes, 1998)

Glass (1959) proposed a useful way of looking at the response of people to catastrophes: the pre-impact period - 'won't happen' (denial); the warning period - inefficient overactivity; the impact period - may be very short - psychological reactions may be limited to automatic responses; the recoil period - underactivity and apathy (as in 'combat fatigue'); and the post-impact period - the most important inefficient behavior patterns are hostility, anger, and resentment, directed against those held directly responsible, towards the government and its organs who may be reckoned to have acted improperly, or could have behaved in a better way, or even towards society in a non-specific way.

There has been an increase in active interest in *dying* patients. Parkes (1978) examined the fears of the dying and believed that while they might be viewed as realistic fears the physician had a role to play. Nurses can help both patients and relatives to express their feelings. The chief fears found were removal from relatives, familiar environment, and occupation, plight of dependants, losing control, crying, or not dying well, being a burden, lack of self-sufficiency because of weakness, and incontinence, confusion, or mutilation. Pain was only a major concern in a few cases. What constitutes a good death varies with the individual, (Saunders et al., 2003) religion and secularism. (Walter, 2003) Spiritual and psychological issues may be paramount for both patient and family. (Jolley & Tapley, 2010) A holistic approach is essential. (Neuberger, 2003)

Kübler-Ross(1970) sequence of attitudes towards dying:

Shock
Guilt
Denial¹⁵⁶⁵
Fear
Anger
Sadness
Bargaining
Acceptance and resignation

Self-help groups for bereaved parents may offer an opportunity to share grief, e.g. Stillbirth and Neonatal Death Society (Irish SANDS).

Shelley (1986) advocated the use of routine assessment of terminally ill patients by a psychiatrist and included social workers and a clerical dimension in the team. Patients with good premorbid personalities who are able to express their feelings are able to cope better. Those with a past history of unresolved painful loss are sensitised to their own potential loss. Most cases feared the process of dying more than death itself; the former process was associated with fears of pain, loss of body function, lack of dignity, as well as being a burden on their families. An unknown fate led to cognitive and emotional confusion. Depression, guilt and anger were common findings. Denial (common) could inhibit emotional resolution or

¹⁵⁶⁴ 1850 60 90 90, jo@samaritans.org, www.samaritans.org.uk. Samaritans founded by Rev. Chad Varah, London 1953.

¹⁵⁶⁵ Weisman (1972, 1974) introduced the term '**middle knowledge**' for the common phenomenon seen in dying patients where they were intellectually aware of their fate and wanted detailed information but at the same time spoke as if they were not dying and did not want to be reminded about this: simultaneous acknowledgement and repudiation. This may become apparent, for example, when there is a recurrence of a fatal disorder. Patients may practice denial to different people at different times, i.e. denial is inconsistent.

even lead to refusal to comply with medical advice. Identification with patients and idealisation, especially of the doctor, were common. Cancer was difficult to cope with because it could not be directly visualised. The staff often felt uncomfortable with emotionally distressed patients and they felt threatened by attempts to discuss the dynamics of their reactions, and they wanted to put the patients on 'rarely needed' antidepressants. Therapists should be aware of their own defence mechanisms. Often, staff distance themselves from the dying by offering false reassurance ('You'll be fine') or by selective inattention ('So your toe is sore?'). Female doctors and those who cared for patients for prolonged periods of time may experience particularly strong emotional reactions to the death of patients, and junior doctors need support from their seniors on such occasions. (Redinbaugh et al., 2003) Yardley and Lunt (1986) reported that nurses looking after dying patients might incur greater stress from their relationships with their colleagues than from issues related to death or dying. Brugh (1993) divided decreased mood in the terminally ill into appropriate and transient feelings of loss and grief, depressive adjustment reaction, and depressive illness, although the distinction between the latter two can be difficult to make in practice. Depression may be under treated in this group for a number of reasons, such as viewing it as appropriate to the circumstances or considering treatment so close to death as being inappropriate. The same care must be taken when explaining antidepressant drugs (and in choosing which one to use) to the dying as is required at other times. The stronger is the religious belief among relatives or friends of a dying person the more quickly and completely is resolution of grieving in survivors. (Walsh et al., 2002) Religious requirements of the dying, including those of minorities, has traditionally been underemphasised in the training of professionals in favour of physical and psychological dimensions of support. (Gatrad et al., 2003)

Keeping the fact that a child is dying from the child and his/her siblings can create many problems for the family. Children often know that they are dying but are rarely asked how they feel about it. (Black, 1998) Religious belief in a soul is helpful. Home-based care is less upsetting than that given in an institution. Survivors need help, support, information, explanation and, if requested, to see the body. Funerals (and wakes) offer a chance to grieve openly.

The *Intensive Care Unit* brought with it a frightening unfamiliarity. The most useful roles of the psychiatrist in the terminal care unit (ICU) are the supervision of psychological care given by other staff, and the direct management of psychiatric complications. The referred cases suffer mainly from cancer. The reasons for referral, in order of frequency, are behaviour problems, depression, anxiety, communication difficulties, possible psychogenic complaints, anticipation of problems (e.g. difficulty in identifying with a nurse/patient, or a histrionic patient), family problems, and in one case 'threatened suicide' (turned out to be a panic attack). The psychiatric diagnoses most frequently made are depression, anxiety, and various acute and chronic organic brain syndromes. The role of environment in causing delirium ('ICU psychosis') is controversial. (APA, 2002, p. 41)

In his *Discourse on Melancholike Diseases* (English trans. 1599) du Laurens reminds us that 'melancholike persons should never be alone'. It was only recently that we began to 'landscape' our ICUs and CCUs with clocks and calendars. The extended family - as distinct from the smaller nuclear family - and the wake with their opportunities for support and for successful grieving are almost things of the past. We should consider Man as a social animal and not as an animal within society.

Near-death experiences have attracted much attention and are of great antiquity.¹⁵⁶⁶ They are often used to support claims for an existence after death. They are probably often experienced by persons who are not close to death. (Roberts and Owen, 1988) The content of such experiences probably tell us little about the experience of death. (Appleby, 1989) There are three groups of features in such experiences: cognitive - distortion of time, review of one's life, panoramic memory; affective - feeling of peace or joy; and transcendental - visual images of a heavenly world. (Greyson, 1985) One can also get feelings of separation from the body, visions of oneself¹⁵⁶⁷, and a 'tunnel experience' of passing through a dark enclosed space to emerge into brilliant light. (Greyson, 1983) Religious conversion experiences may follow temporal lobe seizures, (Dewhurst and Beard, 1970) or sometimes after a near death experience. They are not found in survivors of cardiac arrest. (Dobson et al., 1971)

¹⁵⁶⁶ The Swiss geologist, Albert Heim (1892) collected the first series of such cases from mountaineers who had survived falls.

¹⁵⁶⁷ These can also occur in states of acute anxiety - autoscopy.

Survivor guilt is present when a person initially is relieved that someone else died instead of him and the feels guilty for having such thoughts. He may believe that he was the one who should have died. There may be difficulties in forming close relationships because of fears of 'betraying' the deceased.

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13

Neuroses, Somatoform & Factitious Disorders

Brian O'Shea

Neuroses

'Neurosis is chameleon-like...Symptoms may be presented to the doctor; problems to the social worker; and sins to the priest'.(Sims, 1985)

'A neurosis is a reaction which would be appropriate at a different time and place'.(Varma, 1989)

'Phobias, obsessions, and compulsions result most frequently from neurotic intrapsychic conflicts, but they also arise in functional or organic mood disorders'.(Sims ea, 2000)

'One of the unfortunate consequences of eliminating...neurosis...has been the need to introduce...co-morbidity'.(Sims, 2003, p. 394)

'Recognition can help the unconscious shoe-horning of free-floating symptoms into the given shape'.(Appignanesi, 2008, p. 36)

The terms 'neurosis' and 'hysteria' are retained here because they are commonly employed in clinical practice, many psychiatrists, not necessarily of a psychoanalytical orientation, do not agree with their eviction, and it is artificial to discuss modern terminology out of its historical context.¹⁵⁶⁸ Benzodiazepines (BZDs) and other anxiolytics may be needed longterm in some psychiatric patients, although care should be taken in certain situations, such as personality disorder or alcohol and substance abuse. Regular review, including discussion with the patient, is recommended. Regarding SSRI doses, the lowest doses are used for panic disorder¹⁵⁶⁹, intermediate doses are used for depression, and the highest doses are used in both obsessive-compulsive disorder and the eating disorders.

The modern term (neurosis) embodies an absence of an organic brain disorder, retention of insight (in touch with external reality), and a personality (whilst often somewhat disordered) that is not grossly abnormal. All neurotic disorders share precipitating, perpetuating and predisposing factors.

'Essential characteristics' of the neuroses (Bateman, 1990)

Patient recognises symptoms as being self-derived

Symptoms have psychological and somatic components

(Unlike acute stress and adjustment reactions) symptoms are out of proportion to external circumstances

Behaviour, social relationships and personality are impaired but usually remain within socially acceptable limits

Insight is retained and the ability to distinguish reality from fantasy is unimpaired

There is no evidence of organic brain disease or damage

¹⁵⁶⁸ This diagnosis entered medical practice in the 17th century. (Shorter, 2005, p. 133) In 1603 Dr Edward Jordan disagreed with King James I's imputation of witchcraft in a woman with strange symptoms, claiming instead that they were of hysterical origin. Jean Fernel of Paris claimed that humans could change into animals by the action of demons (lycanthropy). Smollius, in 1610, used the term hypochondriasis because of the belief that certain mental states were due to subchondral organ (liver, spleen) dysfunction. Falret, in 1822, used the same term to mean an abnormal belief about one's health. Thomas Willis, in 1667, stated that the origin of hysteria was not in the womb, as was the then current theory, but rather in the brain. Jean-Martin Charcot of Paris described *la petite* ('minor': longlasting stigmata such as visual and sensory phenomena) and *la grande* (dramatic outbursts, e.g. strange postures) *hystérie* during late nineteenth century. Thomas Buzzard (1890) was convinced that a 'very large number' of hysteria cases had early multiple sclerosis. In 1772 the term 'neurosis' was used for the first time. (Sims, 1985) In 1784 William Cullen included many diverse disorders under the heading of neurosis - any abnormality of sensation and behaviour where there was no pyrexia or observable lesion. Jeremy Bentham, philosopher and lawyer of the early nineteenth century, believed that we express those motives and desires that we find to be unacceptable to us in a disguised or symbolic way. George Beard, an American psychiatrist, described 'neurasthenia' (mental exhaustion) in 1869. It has been suggested that neurasthenia arose in a setting of increased preoccupation with commerce and material success and major changes in the role of women.

¹⁵⁶⁹ Start low to avoid exacerbating anxiety - higher doses than used for depression may be required later.

The 'neuroses' were not included in DSM III because of its association with psychoanalysis. In a large study of diagnoses in a population of 300,000 people in general practice carried out in the early 1970s in Britain the consultation rate for all neurotic states was 75.5/1,000/year for men and 162.9/1,000/year for women, giving a rate of over 90% for neuroses amongst all psychiatric diagnoses. The neuroses were found to be very common among the inpatients and outpatients of hospital specialities other than psychiatry, e.g. 15-20% of hospital presentations in the eye clinic. Two-thirds of psychiatric cases seen in general practices were diagnosable as neurotic during the 1960s.

Neuroses commonly presented with individual symptoms, the undifferentiated syndrome being a form commonly seen in general practice, psychiatrists more usually seeing specific syndromes, although diagnostic instability over time is very common. (Tyrer ea, 2004) Only 36% of cases had no DSM diagnosis after 12 years in Tyrer ea. (2004) The commoner manifestations of the undifferentiated form were anxiety, depression, irritability, insomnia, and fatigue. and preferred the term 'general neurotic syndrome', which ran a prolonged course with variation in the predominance of different neurotic symptoms over time. (see Tyrer ea, 2004) Those with higher PSE scores at initial assessment were usually diagnosed as phobic or depressive, and those with lower scores were diagnosed as having anxiety neurosis. Tyrer ea (2004) found that combined anxiety-depression (so-called 'cothymia'), personality disorder, recurrent episodes, and greater baseline self-rated and depression ratings augured a worse outcome at 12 years, whereas initial diagnosis added little to differences in outcome.

The Office of Population Censuses and Survey (OPCS) in Great Britain carried out a survey of prevalence of psychiatric morbidity among adults (16-64 years) living in private households during 1993 using the *Clinical Interview Schedule – Revised*. (Lewis & Pelosi, 1990) 14% of people had a neurotic problem (12 or more on the schedule), females significantly outnumbering males. The most common symptoms were fatigue (27%), sleep problems (25%), irritability (22%), and worry (20%). The most prevalent ICD-10 neurotic disorder was mixed anxiety and depressive disorder¹⁵⁷⁰ (7.7%) followed by generalised anxiety disorder (GAD, 3.1%¹⁵⁷¹). (Mason & Wilkinson, 1996)

National Comorbidity Survey Replication: general population life time/past year (Kessler ea, 2005)

Any anxiety disorder	31.2/18.7
Specific phobia	12.5/8.7
Social phobia	12.1/6.8
PTSD	6.8/3.6
GAD	5.7/2.7
Panic disorder	4.7/2.7
OCD	1.8/1.1
AWP	1.3/0.8

Key: AWP, agoraphobia without panic; GAD, generalised anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

5-HT₂ receptors may be upregulated in depression and downregulated by antidepressant drugs like SSRIs and TCAs. However, both antipsychotic drugs and LSD also downregulate these receptors, and ECT upregulates them!

Annual cost of anxiety disorders to US economy (Greenberg ea, 1999)

Total - about \$42.3 bn
General medical treatment - \$23 bn
Psychiatric treatment - \$13.3 bn
Indirect workplace - \$4.1 bn
Mortality - \$1.2 bn

¹⁵⁷⁰ The 1-month prevalence of 'mixed anxiety and depression' (lower overall symptom count than ICD-10 anxiety and depression) was 8.8% in a British household sample of 16-74 year olds. (Das-Munshi ea, 2008)

¹⁵⁷¹ According to Kelsey ea, (2006, pp. 145-6) estimates of lifetime prevalence of GAD vary from 4-9%, usually starting in adolescence/early adulthood. It should be noted, however, that, during a given year, 3-7% of children fulfil criteria for overanxious disorder of childhood.

The main theories of causation of neurotic disorders are introduced in the box and discussed further under individual syndromes.

Aetiology of neuroses

Neurotransmitters: Attenuation of GABA leads to anxiety. 5-HT_{2c} receptors may be activated by stress. Antidepressants eventually downregulate 5-HT_{2c} receptors. Buspirone stimulates 5-HT_{1a} autoreceptors (availability of which are reduced in panic disorder: Nash et al, 2008); this reduces 5-HT release which may then switch off the 5-HT_{2c} anxiety signal. Stress increases norepinephrine release.

Behavioural: Maladaptive activity, exaggerated affect, inability to change, preservation of insight; aware behaviour is irrational and inappropriate but feels unable to stop it; learned phenomenon. However, neurotic (emotionally reactive temperament) behaviour often persists without any obvious reinforcement. The early learning theories of Pavlov and Skinner cannot account fully for human learning. Since then there has been increased attention to cognitions intermediate between stimulus and response. Does behaviour therapy work because it mobilises changes in the client's attitudes about himself in relation to his difficulty, rather than because of some conditioning mechanism? (Mackay, 1992)

Psychoanalytic: More appropriate to earlier stage of psychosexual development; fixed at some earlier stage - this becomes obvious under stress; inappropriate and excessive use of defence mechanisms to reduce anxiety; exaggeration of normality. Freud believed that children were aware of only one sexual organ, the penis. It has been suggested that his phallic phase should be renamed the infantile genital stage, the adult genital stage not commencing until puberty. Panic disorder and agoraphobia have been ascribed to parental, especially maternal, loss or separation in childhood – finding oneself in the open, alone, revives memories of the earlier loss.

Sleep: It is interesting to note that panic attacks in panic disorder can occur at night, in one study only during non-REM sleep. (Mellman & Uhde, 1989)

Genes: Anxiety disorder commoner in relatives than in the general population; 41% of MZ and only 4% of DZ twins concordant for anxiety disorder; in support of a genetic input was a study by Lader and Wing (1966) of the reactivity of the autonomic nervous system as measured by the rate of habituation of the galvanic skin response (GSR). Use of hospital-based samples rather than a wider range of anxiety problems in the community at large may have biased early studies. A later twin study suggested that what is inherited is a non-specific tendency to develop neurosis in general and that the environment may then determine the subtype. (Torgersen, 1983; see Andrews, 1996) It is instructive to recall that an initial report of linkage of panic disorder to a locus on chromosome 16 was refuted by the same team! 95% of panic disorder patients and 7% of the general population were found to possess a duplication (DUP25) on chromosome 15 by Gratacos et al (2001) but this finding was not replicated by Schumacher et al. (2003) Polymorphisms of the serotonin transporter gene may provide a link between major depression and generalised anxiety disorder. (Ohara et al, 1999) MZ twins are more alike regarding the patterns of their fears than are DZ twins when tested by questionnaire. (Torgersen, 1979) Murray et al (1981), using the LOI, suggested heritabilities of 0.44 for obsessional traits and 0.47 for obsessional states. A number of authors have decried the abandonment of the concept of endogenous anxiety and some put the blame on excessive homage to Cartesian dogma. According to Kendler, (1996) twin studies suggest the identical or similar genes predispose to generalised anxiety disorder and major depression. Hettner et al (2005) suggest that genes predispose to two broad groups of disorders: panic-generalised-agoraphobic anxiety on the one hand and specific phobias on the other, with social phobia being influenced by both genetic factors. A variant of a gene encoding plexin A2 (PLXNA2) may be associated with anxiety. (Wray et al, 2007) The reader is referred to the section dedicated to individual anxiety disorders for further discussion.

Childhood neurosis: Does not necessarily lead to adult neurosis. A far stronger indicator of adult psychological problems is socially unacceptable behaviour in the child. If childhood neurosis does persist it is usually as either a neurosis or a depressive state. Murray et al (2009) stress the importance of parent-child bidirectional influences in the development of anxiety disorders in children: various characteristics (temperamental style of behavioural inhibition or biases in information processing) may constitute inherited vulnerabilities; environmental factors such as adverse life events and exposure to negative information or

(parental) role models; and over-protection of children by anxious parents as a response to characteristics displayed by the child.

Family interactions: Women allegedly 'pick up' neurosis more readily from their husbands than vice versa, although changing social roles may modify this. The strains of an unsatisfactory family life might militate against women more than men. Men were said to turn to alcohol or criminality, but incidence and prevalence of female alcoholism is increasing. Women often become depressed when the children leave home - empty nest syndrome. Neurotic men stay with their wives for more time than non-neurotic men, i.e. they fail to socialise. (Krietman ea, 1970)

Experimental neurosis: Frustration breeds neurotic behaviour in animals - the executive monkey also develops ulcers; degree of stress required is probably greater in less 'neurotic' personalities.

Dissociation disorders: There is splitting off of pathogenic material from conscious awareness; this material nevertheless continues to exert an influence. Janet wrote of state-dependent memory behaviour where events could only be recalled under similar emotional circumstances. Breuer emphasised autohypnosis. Freud described repression and other defences. Abnormal temporal lobe function has been proposed. Iatrogenesis blames therapist suggestion. Earlier abuse, including CSA, is an attractive theory, but no linear causal relationship has been proven. Nevertheless there is some evidence for an association between childhood interpersonal trauma as a whole, and emotional abuse in particular, predisposing to dissociation and depersonalisation disorder in adulthood. (Simeon ea, 2001) Malingering and factitious depersonalisation complete the list of candidates. In practice, dissociation may exist on a spectrum with normal levels at one end and more obviously pathological degrees at the other extreme. Younger people, particularly children, may be more likely to dissociate and to meet criteria for dissociative disorders.

Sociological: Labelling theory (Scheff, Erikson) - people act in assigned ways; doctors are medical police, labelling deviancy as illness. Sick role theory (Parsons) - the advantages of sick role leads to its adoption. Deviance (Lemert) - primary deviance consists of behaviour that initially prompts medical referral, secondary deviance consists of improper advantage taken by the patient of his illness. Socio-cultural factors might account for Orley and Wing's (1979) finding of twice as much neurosis among Ugandan women as among London women.

The patient would say that he felt unwell. 'Depression' and 'unable to cope' were common calling cards. Social function was poor, activities being disorganised by affective disturbance. Coping with trivia was particularly unsuccessful. Non-competitiveness followed from low self-esteem. The patient was fearful, felt inferior, and was racked by shame. There was profound difficulty in enjoying simple things, and overcompensation was common. The sufferer's attitudes varied more than is normal and, because of constant tension, tiredness and listlessness were more or less constant.

Neurotics were known to have a high morbidity. Follow-up of 'hysterics' was said to reveal a high incidence of neurological disease, although these findings have been challenged because the cases seen may have been self-selected since most of them attended neurological centres. Not all studies find organic problems at follow up and re-assessment should probably not be undertaken unless clearly clinically indicated; the advent of neuroimaging may have assisted in reducing the number of cases incorrectly assigned a diagnosis of hysteria. The diagnosis of an 'hysterical disorder' is not one of exclusion - positive evidence for the presence of neurosis must be sought.

Some historical neurotic syndromes

Neurotic depression: Over two-thirds of anxiety disorder patients will develop a mood disorder, particularly depression, during life. (Pigott & Lac, 2002)

In *anxiety neurosis*¹⁵⁷², the trigger may be environmental or symbolic. Freud believed that anxiety could arise from the external world, the Id (unacceptable drives) or the Super-ego (moral constraints). Anxiety may be the predominant neurotic symptom. An anxiety state (circumscribed, occupies a definite period of time; may be recurrent) must be distinguished from an anxiety trait (always an anxious person). Free-floating anxiety infers that no specific focus for the anxiety can be found (? may have generalised from an attachment to a specific stimulus). Fear is elicited by an objective threat; anxiety is said to arise from unconscious conflicts with no objective stimulus.

¹⁵⁷² Freud's *anxiety (actual) neurosis* concept included general irritability, chronic apprehension, attacks of anxiety, and secondary phobic anxiety.

*Writer's cramp*¹⁵⁷³ is one of the 'occupational cramps', 'task-specific dystonias' or 'craft neuroses'. These conditions share the impairment or loss of a learned motor skill¹⁵⁷⁴. The features of writer's cramp are muscle spasm, ataxia, and discomfort when trying to write¹⁵⁷⁵. The clinical picture is very variable. It may be chronic and progressive with fluctuations in intensity, or it may stop spontaneously at any stage. The subject finds it difficult or impossible to write. Treatment strategies varied historically from electric shocks through re-education and exercises to psychotherapeutic analysis of hostility. Our poor state of knowledge was illustrated by the reporting of 8 out of 42 patients with torsion dystonia that commenced with writer's cramp. In fact, writer's cramp is a focal dystonia, a neurological disorder with equal sex incidence and commencing in adulthood. There is abnormal interneuronal function in the spinal cord. Five percent of cases are familial and possibly autosomal dominant with reduced penetrance. Treatment is difficult, e.g. changing the way a person writes or injections of Botulinum toxin into affected muscles. Spontaneous remission is uncommon. (Thompson, 1993)

*Irritable heart*¹⁵⁷⁶ was described by da Costa during the America Civil War (his first case had aphonia lasting for 10 months). The patient is free of heart disease, is convinced that he has such a disease, and complains of palpitations, fatigue, and inframammary pain. The cause is an anxiety neurosis with hyperventilation. Fiorentini ea (1981) found beta-blockers to be useful in controlling the symptoms. Physicians more recently described a 'condition' called pseudoangina that they say is due to exhaustion!

Hypochondriasis could be divided into primary¹⁵⁷⁷ and secondary. It was strongly debated whether so-called 'primary' cases existed as a neurosis or whether they more correctly came under the heading of personality disorder. The neurotic form had its enthusiastic champions. The secondary form was most often a manifestation of depression - other causes were anxiety states (incl. panic disorder: Noyes ea, 1986; Nutt ea, 2002, p. 11), schizophrenia and dementia. Rapid improvement in cases of illness phobia and hypochondriasis was reported in an uncontrolled trial by exposing patients to illness cues (e.g. exercising to try to bring on a heart attack, or reading literature on the feared illness) and banning of reassurance - seeking behaviour (e.g. no visits to hospital for tests, and relatives not to give reassurance when that is requested).

Hysteria: In hysteria, the primary gain resulted from anxiety reduction as a result of adopting a hysterical defence. Secondary gain was the avoidance of some anxiety-provoking situation. Prognosis was worsened if the personality was disordered, there was somatisation disorder (Briquet's syndrome), if there was much secondary gain, and if the illness was perpetuated by environmental circumstances. Analytically speaking, hysterical reactions are unconscious, i.e. they are not malingering - in the latter instance the 'patient' is fully conscious of what he is doing and why he is doing so. One point against the anxiety-reduction model was the finding of increased muscle tone with the EMG in hysterical conversion states, i.e. hysterics have high arousal levels and very low habituation in spite of low overt anxiety. DSM-III divided hysteria into somatoform disorder (hysteria with mainly physical symptoms; also includes hypochondriasis), dissociative disorder (hysteria with mainly psychological symptoms; also includes depersonalisation disorder), and factitious disorders (uncommon self-inflicted disorders). Dooley (1986) viewed hysteria as a form of behaviour rather than as a disease. As a diagnosis it had declined greatly among inpatients and outpatients in the West and in Japan since the middle of the twentieth century, but it still appeared to be common in underdeveloped areas. During WWII, British and Indian soldiers presented more often with anxiety and hysteria respectively. Conversion hysteria was still common in Indian clinics in the late 1980s, where diazepam was preferred to barbiturates in abreaction interviews. However, hysteria had declined significantly in rural Bengal by 1992. The ancient Greeks believed that hysteria was confined to females and resulted from the migrations of the womb¹⁵⁷⁸ about the body, the womb becoming stuck somewhere and leading to problems. As a lay term which it is synonymous with histrionic. Hysterical personalities were self-centred and demonstrative, incapable of deep emotional commitments. Its presence did not greatly increase the likelihood of developing any other 'form' of hysteria. Hysteria is sometimes seen as a mainly female disorder with antisocial personality as its equivalent in males. Some cases of 'epidemic hysteria' have been described where one person caused outbreaks at different schools! Akagi and House (2002) suggest that most cases of hysteria are not seen by psychiatrists, that it has not really gone away, that there are problems of definition and scope, and that acute and transient cases may be missed. In fact, most modern major psychiatric epidemiological studies, such as the British Psychiatric Morbidity Study, (Jenkins ea, 1997) have not attempted to identify hysteria.

Conversion hysteria was said to have become relatively uncommon in recent years but Ford (2008a, p. 396) suggests that they have simply become more subtle and sophisticated unlike 'the dramatic symptoms of the past'. Almost any physical ailment might be represented, especially paresis and blindness. The patient appeared to 'convert' anxiety into a somatic disorder. Conditions like *globus hystericus* (lump in the throat) and torticollis were shown to have a high association with physical illness. Treatment might take the form of psychoanalysis, waiting, hypnosis, the presentation of strong odours in the case of 'anosmia', placebo, psychotherapy, or even sham physiotherapy. In *globus hystericus* ('*globus pharyngis*') the patient feared that he was intermittently choking and unable to breathe; he can sense a lump in his throat; it is not related to swallowing, and can sometimes be relieved by swallowing liquids or solids. Globus pharyngis was reported to be associated with elevated BDI depression scores and recent independent life events and to respond to tricyclic antidepressants and to MAOIs. It was known that hysterical symptoms, e.g. global amnesia, could be 'released' by organic brain disease. Great caution was urged in making a diagnosis of hysteria. In one study (Maurice-Williams & Marsh, 1985) of 14 cases of simulated paraplegics and tetraplegics it was considered that it was rarely possible to determine whether the behaviour was conscious or not. In most cases the paralysis was of short duration and recovered quickly with simple methods of treatment (e.g. chlorpromazine, firm reassurance, and placebo injections). Many such cases probably never come to the attention of psychiatrists.

¹⁵⁷³ Scrivener's palsy, graphic dyskinesia, *crampe des écrivains*, *mogigraphie*, or *fingerkrampf*.

¹⁵⁷⁴ Merskey and Mai (2005, p. 5) suggest that **repetitive use (strain) injuries** (RSI) are usually regarded as 'aberrant habits of muscular usage' rather than motivated loss of function. There is some evidence that hypnosis may reduce pain in the short term in RSI and little evidence for the effectiveness of special keyboards and other ergonomic interventions. (Page & Wessely, 2007, p. 140)

¹⁵⁷⁵ Patients with occupational dystonias may be dismissed as exaggerating their problems because they can perform one task (say use a typewriter) and not another (e.g. play a piece on the piano).

¹⁵⁷⁶ Cardiac neurosis, disorderly action of the heart, effort syndrome of Lewis, neurocirculatory asthenia of Oppenheimer.

¹⁵⁷⁷ A difficult condition to treat, full of concerns for one's health, often resistant to reassurance, often having many hospitalisations and investigations.

¹⁵⁷⁸ *L. uterus*; Gk. *hyster*.

Shalev and Munitz (1986) suggest a re-definition of conversion as 'A variety of illness behaviours, characterised by unexplained symptoms, suggesting a neurological disease, occurring in a wide variety of medical and psychological disorders' (i.e. treat the actual source of distress and stop interpreting analytically). Merskey (1986) advised that if a hysterical patient says that both of his lower limbs are paralysed the examiner should put his hand under one heel and ask him to raise the other leg - the examiner will feel the heel pressing into the ground. In cases of feigned unilateral lower limb weakness, with the patient supine, the *Hoover sign* is positive if there is no downward pressure exerted by the unaffected leg when an attempt is made to lift the affected leg¹⁵⁷⁹.

Camptocormia (curved trunk), a rare largely wartime conversion syndrome resembling a simian posture was described independently in 1916 by Souques and Rosanoff-Saloff. The features include frontal vertebral flexion, passive drooping of the arms, variable genuflexion, and ataxia. Flexion increases on walking, disappearing when recumbent. The posture was probably worsened by stooped walking in trenches. Organic causes exist, e.g. spinal cord or vertebral lesions, Parkinson's disease, and, in one complicated case, sodium valproate. (Kellett & Chadwick, 2004, p. 332) This author has seen cases resembling camptocormia in people on antipsychotic medication.

Dissociative hysteria might involve clouding of consciousness and a loss of memory for events occurring during an episode. Examples are trances and fugues. DSM-III defined dissociative disorders (psychogenic amnesia, psychogenic fugue, and multiple personality) as being characterised by a sudden, temporary change in the normally integrated function of conscious identity, or motor behaviour, so that some part of one or more of these functions is lost.

As Nutt et al (2002, p. 7) point out, DSM-IV is non-hierarchical¹⁵⁸⁰ whereas agoraphobia, social phobia and specific phobia take precedence over panic disorder, i.e. social phobia + panic attacks = social phobia. Lindsay (2008, p. 574) take issue with high US prevalence figures for phobic disorders and suggests that they may be artefacts of diagnostic criteria or rules governing severity thresholds and disorder hierarchies.

Modern classification of neurotic disorders

(a) ICD-10: Neurotic, stress-related and somatoform disorders

F40: Phobic anxiety disorders – divided into agoraphobia, social phobia, specific (isolated) phobias, 'other', and 'unspecified'.

F41: Other anxiety disorders – panic disorder (episodic paroxysmal anxiety), generalised anxiety disorder (GAD), mixed anxiety and depressive disorders (common in general practice), 'other', 'other specified', and 'unspecified'.

F42: Obsessive-compulsive disorder (OCD) – predominantly obsessional thoughts or ruminations, predominantly compulsive acts (obsessional rituals), mixed thoughts and acts, 'other', and 'unspecified'.

F43: Reaction to severe stress, and adjustment disorders – acute stress reaction, post-traumatic stress disorder (PTSD), adjustment disorders (includes culture shock, grief reaction, and hospitalism in children, but excludes separation disorder of childhood – various subtypes depending on duration, and main emotions and/or conduct effects), other reactions to severe stress, and the usual 'unspecified' ragbag.

F44: Dissociative (conversion) disorder (partial or complete loss of normal integration between memories of the past, awareness of identity and immediate sensations, and control of body movements – dissociative amnesia (loss of memory, usually of important recent events/personal information [including those of a criminal, sexual, marital, or financial nature], not organic in origin and too extensive to be blamed on ordinary forgetting or fatigue), dissociative fugue (dissociative amnesia plus an apparently purposeful journey away from home/work during which self-care is maintained; more common following natural catastrophes or during war; patient may become upset when questioned about personal history), trance and possession disorders (temporary loss of both the sense of personal identity and full awareness of the surroundings; may act as if taken over by another personality, deity, or 'force'), dissociative disorders of movement and sensation (loss of/interference with movements/sensation, not explicable by somatic medical knowledge – some people react repetitively to stress in this way; dissociative movement disorders (e.g. paralysis, ataxia, apraxia, etc not explicable somatic medical knowledge), dissociative convulsions or hysterical pseudoseizures, dissociative anaesthesia and sensory loss, an 'mixed' cases), and 'others' such as Ganser's syndrome (giving 'approximate answers'), or multiple personality disorder. There are also transient such disorders found in children/adolescents, and a ragbag 'other' category (psychogenic confusion and the twilight state).

¹⁵⁷⁹ This *sign* or *test* can also be stated as consisting of downward pressure on the affected leg when the patient tries to raise the unaffected leg. Pressure arises from synergistic muscular contraction. The examiner's hand is held under the heel that is not being raised.

¹⁵⁸⁰ One can diagnose more than one anxiety disorder simultaneously in the same patient.

F45: Somatoform disorders – repeated presentation of physical symptoms and requests for medical investigations, negative findings, and failure of reassurance. Divided into somatisation disorder (complains of symptoms), undifferentiated cases, hypochondriacal disorder (complains about having a serious and progressive disease), somatoform autonomic disorder (symptoms suggesting disease of body part or system that is innervated by the autonomic nervous system, e.g. ‘gastric neurosis’, ‘cardiac neurosis’, ‘nervous diarrhoea’, psychogenic hiccough, and psychogenic hyperventilation), and ‘persistent’, ‘other’, and ‘unspecified’.

F48: Other neurotic disorders, i.e. neurasthenia (weakness, fatigue, and various psychosomatic symptoms like dizziness or dyspepsia; a common diagnosis in China; includes ‘fatigue syndrome’), depersonalisation-derealisation disorder (where these are the predominant complaints; ICD-10 states that they resemble ‘near-death experiences’), ‘other’ (e.g. Briquet’s syndrome, dhat, koro, latah, occupational neuroses like writer’s cramp, psychasthenia, and psychogenic syncope), and ‘unspecified’.

(b) DSM-IV: Anxiety disorders

A single panic attack¹⁵⁸¹ cannot be coded (vide infra)

Agoraphobia

Panic disorder (recurrent panic) without/with agoraphobia

Agoraphobia without history of panic disorder

Specific phobia (formerly simple phobia)

Social phobia (social anxiety disorder)

OCD

PTSD (re-experiencing of extremely traumatic event plus symptoms of increased arousal and avoidance of stimuli associated with the trauma)

Generalised anxiety disorder (GAD: at least 6 months of persistent and excessive anxiety and worry – includes overanxious disorder of childhood)

Anxiety disorder due to general medical condition/substance-induced

(c) DSM-IV: Somatoform disorders

Presence of physical symptoms suggesting but not explained by general medical condition – also not explained by substance effects or another psychiatric disorder like panic disorder:

1. Somatisation disorder (‘hysteria’, ‘Briquet’s syndrome’) – polysymptomatic condition starting before age 30 years, extending over a period of years, and characterised by a combination of pain, GIT, sexual and pseudoneurological symptoms
2. Undifferentiated somatoform disorder – unexplained physical complaints of at least 6 months duration, below threshold for 1. above
3. Conversion disorder (*vide infra*)
4. Pain disorder¹⁵⁸² – descriptions are often dramatic and vivid and pain ‘explains’ all difficulties
5. Hypochondriasis – preoccupation with fear of having, or the idea that one has, a serious disease based on the person’s misinterpretation of bodily symptoms/functions

(d) DSM-IV: Factitious disorders

Physical or psychological symptoms intentionally produced/feigned to assume sick role; not due to malingering (intentional production of symptoms with goal that is obvious when environmental circumstances are known, e.g. to collect insurance); motivation is a psychological need to assume sick role; absence of external incentives for behaviour; divided into –

1. with predominantly psychological symptoms/signs
2. with predominantly physical symptoms/signs
3. with combined psychological and physical symptoms/signs

(e) DSM-IV: Dissociative disorders (*vide infra*)

Somatisation disorder

As a phenomenon, the most common psychiatric disorders that are associated with somatisation are not the somatoform disorders, but rather depression, panic and adjustment disorders. Undifferentiated somatoform

¹⁵⁸¹ Some people experience panic as a normal reaction to significant threat, e.g. combat.

¹⁵⁸² Co-morbid personality disorder is common, especially histrionic, dependent, and passive-aggressive.

disorder (DSM-IV-TR; also called 'multisomatoform' disorder) is probably the commonest somatoform disorder in the community in the USA¹⁵⁸³.

DSM-IV-TR criteria for somatisation disorder are simply a shortened version of Guze's original criteria for Briquet's syndrome¹⁵⁸⁴. It is not true that these patients only complain of (multiple and unexplained) physical symptoms, complaints of psychological ('psychoform' symptoms) and interpersonal difficulties being quite common. The MMPI may mimic multiple psychiatric disorders in such patients. Many psychiatrists believe that this disorder and hypochondriasis, because of their intransigence and longevity, best belong with the disorders of personality. In fact, there have been reports of excess of antisocial personality disorder in first-degree relatives of patients with somatisation disorder. (Lilienfeld *et al.*, 1986) Various theories concerning the origin of adult somatisation have been proposed, e.g. lack of parental care during childhood followed by childhood illness, i.e. being ill becomes a powerful form of communication and commands attention; childhood hospitalisation; illness in significant others; (Craig *et al.*, 2002) and CSA. Stern *et al.*'s (1993) controlled study of females with somatisation disorder reported an excess of personality disorder, especially passive-dependent, histrionic, and 'sensitive-aggressive'. According to Martin *et al.*, (1985) attempted suicide is common, but not suicide itself.

Patients with somatisation disorder are inconsistent historians. (Yutzky, 2003)

Complaints vary and may be forgotten between consultations. Details can be elusive and inconsistent. Efforts at clarifying vague complaints may leave the clinician confused. Exaggeration is common, e.g. 'I bled for days'. The style is histrionic (unlike the hypochondriac who tends to be obsessional). A sense of urgency pervades presentations. Patients may have co-morbid depression¹⁵⁸⁵, anxiety, parasuicidal tendencies, and drug abuse.

Cloninger (1994) suggests that the best discriminators between somatisation disorder and somatic illness, in cases where thorough investigation leaves aetiology obscure, are multiple organ involvement, early onset and chronic course but no physical signs related to abnormalities of structure, and no characteristic laboratory abnormalities of suggested physical disorder. MS, SLE, acute intermittent porphyria, and haemochromatosis may be mistaken for somatisation disorder. Cloninger (1994) considers anxiety disorders, affective disorders, and schizophrenia¹⁵⁸⁶, to be the main psychiatric disorders that may mimic somatisation disorder. He states that histrionic traits, sexual/menstrual problems, and social impairment support a diagnosis of somatisation disorder. The psychiatrist should read the patient's medical records¹⁵⁸⁷. Bass and May (2002) provide a useful overview of somatisation disorder under the heading of 'chronic multiple functional somatic symptoms' (CMFS). According to these authors, over 4% of the general population and 9% of tertiary care referrals have this syndrome. Each GP has 10-15 cases. The actual prevalence varies with the number of symptoms required for a diagnosis. Most cases are female, although reducing the number of symptoms required and eliminating female-specific symptoms (e.g. menstrual) greatly decreases the female-male divide. Recurrent depression, chronic interpersonal difficulties¹⁵⁸⁸, drug abuse, an emotionally deprived childhood, and physical or sexual abuse as a child are commonly recorded. Other characteristics are a disturbed personality and voluminous case notes. They suggest regular (if infrequent) and scheduled (not dependent on symptoms) interviews, focused physical examination, avoidance of excessive tests, (Ring *et al.*, 2004) avoiding accumulation of drug treatments (taper as needed), diplomatic reframing (re-attribution) of somatic complaints by linking them to life circumstances, use of problem lists, coopting a relative as a therapeutic ally, aiming at coping (not curing), examination of maintaining factors¹⁵⁸⁹, and remembering that a poor relationship with the therapist may reflect poor parental care/emotional deprivation in childhood. Instead of trying to sell a single aetiology to the patient,

¹⁵⁸³ Page and Wessely (2007, p. 128) argue that symptom overlap and heterogeneity with individual syndromes suggest that functional somatic syndromes are not discrete conditions and may be products of medical specialisation.

¹⁵⁸⁴ Although DSM requires onset before age 30 years, most cases have some symptoms by adolescence or early adulthood, full criteria been met by the mid-twenties. Pierre Briquet (1796-1881) wrote a book on hysteria (1859) while working at the Charité Hospital in Paris.

¹⁵⁸⁵ It has been questioned whether such patients actually have a disorder called depression or simply complain excessively. (Yutzky & Parish, 2008, p. 617)

¹⁵⁸⁶ A large chunk of psychiatry! Patients with somatisation disorder may panic or be depressed, and somatisation may sometimes precede schizophrenic breakdown.

¹⁵⁸⁷ Not all of which may be available in one site.

¹⁵⁸⁸ It is not uncommon for affected females to marry antisocial males and to be rather inadequate parents themselves.

¹⁵⁸⁹ E.g. depression, dependency needs, marital problems, or medico-legal claims.

the clinician should help him or her to understand how many interacting factors (genes, personality style, and life events influence physiology) interweave to produce current circumstances. This approach opens up multiple avenues for intervention (Kontos & Querques, 2008, p.757). However, after training in reattribution, GPs have been shown to give mixed psychosocial and somatic messages (possibly making patients' worries about physical illness worse) to patients and not to probe for underlying psychosocial issues.(Morris ea, 2010)

Hypochondriasis¹⁵⁹⁰

Hypochondriasis is most likely non-categorical. It varies along a continuum of severity¹⁵⁹¹, with or without overvalued ideas, e.g. milder cases seen by GPs may be receptive to reassurance, at least transiently. Hypochondriasis has been seen as a neurosis, a personality disorder¹⁵⁹², a depressive equivalent, a bereavement reaction, and a variant of OCD. There is no rule preventing the one patient having features of somatisation disorder, conversion disorder, and hypochondriasis. There is little evidence for genetic transmission in hypochondriasis. Childhood factors include abuse, neglect, and positive feedback during illness. Interpersonally, it is a form of care-eliciting behaviour. There may be symptom identification with deceased relatives. Culture may add to the problem by an emphasis on keeping super-fit, although hypochondriacs are not noted for taking precautions against health hazards like quitting smoking or taking a proper diet¹⁵⁹³.(Fava & Grandi, 1991) There may be a tendency to misinterpret bodily sensations as disease. Sufferers check themselves repeatedly in mirrors, feel the pulse, or look up medical sources (books, *MIMS*, *PDR*, *Merck Manual*, Internet, etc.) looking for information. They may keep their own medical records. They fear getting old and dying. The differential diagnosis is wide and includes illness phobia¹⁵⁹⁴ and delusional disorder, somatic type¹⁵⁹⁵. The patient classically relates her tale in excessive detail but without emotion (unlike the drama of somatisation disorder). Emotional life is constricted. Social, occupational and sexual activity is limited.

CBT helps, at least in the short term, compared to waiting list controls. SSRIs have also been advocated.(Noyes, 2005; Greeven ea, 2007)

Surprisingly, hypochondriac patients may deal with actual somatic disease realistically! The symptoms wax and wane over time, becoming worse when the patient is stressed. Media coverage of illness or hearing of illness in another person may exacerbate health concerns.

Multiple personality disorder (MPD)

MPD (*dissociative identity disorder* in DSM-IV-TR)¹⁵⁹⁶ is characterised by the appearance of more than one personality, each one, supposedly, being unaware (consciously) or only partially aware of the others' existence.(O'Shea, 2000a) The term *alter* refers to another personality whereas *co-consciousness* refers to the simultaneous awareness of multiple personalities. There may be marked mood changes, changes in

¹⁵⁹⁰ ICD-10 but not DSM-IV includes dysmorphophobia under this rubric.

¹⁵⁹¹ The concept of 'health anxiety' is much broader than that of hypochondriasis.(Rief ea, 2001) Life events, including somatic illness, may provoke short-lived hypochondriasis. Persistent cases may relate to comorbidity with axes I and/or II disorders.(Kirmayer & Looper, p. 425) Health anxiety, as in concern/anxiousness re possible disease, was associated with frequent consultation in a two-practice Dublin study.(Conroy ea, 1999) 'Medically unexplained syndromes' (MUS) is a common phenomenon in GP and, although variously defined, usually refers to complaints that have no established somatic or psychosocial origin. Underlying disorders include pain due to depression, the physical symptoms of anxiety, and undifferentiated somatoform disorder.

¹⁵⁹² No specific type is associated with this disorder. Symptoms, e.g. distrusting doctors, could equally be viewed as symptoms.

¹⁵⁹³ Perhaps believing one has a serious disease and a foreshortened future renders healthy change appear redundant.

¹⁵⁹⁴ Fear of developing as distinct from having a disease, as when a person unreasonably fears developing AIDS on being exposed to someone with that condition. The unreasonableness is clearly recognised by the patient and somatic symptoms are not a major component. There is fear or discomfort on being exposed to thoughts of illness. A community survey found illness phobia in 5% of subjects.(Noyes ea, 2000)

¹⁵⁹⁵ Delusions are often bizarre/unrealistic.

¹⁵⁹⁶ Sims (2003, p. 221) suggests that *person or persona* (L. mask) may be a better term than personality when applied to MPD. Mitchill may have described the first case in 1816: Mary Reynolds, an English woman in Pennsylvania. The Bordeaux asylum surgeon Eugène Azam (1822-99) described the case of Félicité, a seamstress, during the 1870s. Her primary personality was 'present' for the birth of her many children but it appears that it was the secondary personality who became pregnant! Probably the most famous case was that of Eve.(Thigpen and Checkley, 1957) FR Schreiber has described the case of Sybil who had 16 personalities. Some authors have reported on as much as 100 'recent cases' and others have discovered it in 3.3% of 299 general adult psychiatric inpatients in a North American teaching hospital. Reporting of individuals with 100 or many more 'personalities' have excited some commentators to suggest that there is a competition afoot! The Californian 'Hillside Strangler', Kenneth Bianchi, faked MPD and hypnosis, and thus fooling psychologists and psychiatrists to avoid capital punishment. Maldonado and Spiegel (2008, p. 683) state that the increased number of reports of MPD are unlikely to be due to suggestion alone and hold that a reduction in misdiagnoses (e.g. schizophrenia) and better recognition of the prevalence and consequences of child abuse are other likely explanations.

handwriting, the idea that unfamiliar people know one, or that unfamiliar objects are found in ones possession. A significant proportion of cases report hearing voices that have an internal origin. Among the characteristics of the alternate personality are various mood states, various attitudes toward the primary personality, the same or opposite sex, or different chronological ages. The criteria have been criticised as vague and overinclusive by Piper.(1994) DSM-IV-TR includes MPD under the dissociative disorders (see below) and is described therein as the presence of 2 or more distinct identities or ‘personality states’ that recurrently take control of the affected person’s behaviour accompanied by an inability to recall important personal information that is too extensive to be explained by ordinary forgetfulness. Pierre Janet described the mechanism dissociation - elements of consciousness split off to assume an autonomous existence which analysts invoke for this and many other hysterical phenomena, such as amnesia and fugue states. A childhood history of significant trauma, especially child physical or sexual abuse (up to 83% claim a CSA history: Yutzy, 2003, p. 678) has been reported, as has fulfilment of criteria for PTSD in adulthood, although the evidence has been strongly criticised.(Piper, 1994) Vermetten *et al.* (2006) found smaller hippocampal and amygdalar volumes in female MPD patients compared to healthy controls. Hypnosis has its enthusiasts as a diagnostic or therapeutic instrument in these cases,(Maldonado & Spiegel, 2003, p. 726) although not everyone would see the wisdom of this approach. The alternate personality tends to be blamed for promiscuity, self-mutilation, etc. Many psychiatrists hold that the disorder is iatrogenic and culturally dependent, whilst others believe that it is induced by media coverage. Merskey (1992) described the diagnosis as a ‘misdirection of effort which hinders the resolution of serious psychological problems in the lives of patients’. He retains the right to diagnose occasional changes in temperament (constitutional tendency to react to stimuli in a particular way; component of personality that is heritable, developmentally stable, based on emotion, and immune to social/cultural influence) or apparent personality style as dissociative in nature. Some authors decry the fact that many years passed before the condition was diagnosed. Cardeña and Gleaves (2007, p. 495) call on disbelievers to prove their point.¹⁵⁹⁷ Conversion symptoms, somatic complaints, malingering, and factitious disorders are not uncommon in MPD cases. Maldonado and Spiegel (2008, p. 684) state that one usually finds evidence of comorbid Axis I and Axis II disorders in MPD patients, especially depression, substance use disorders, and borderline personality disorder, as well as self-mutilation. They also state (p.698) that dissociation occurs worldwide but is more likely to take the form of MPD in the West and possession states in the East.

Dissociative disorder

DSM-IV-TR defines dissociative disorders as disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment. It may be of sudden or gradual onset, transient or chronic. There are 4 subtypes. In dissociative (psychogenic) amnesia¹⁵⁹⁸ the person cannot recall important personal information, usually of a traumatic or stressful nature, and the amnesia is too extensive to be explained by ordinary forgetting. Freeman (1993) wrote that ‘it is probably impossible to distinguish [hysterical] amnesias from conscious malingering unless the patient confesses’. In dissociative (psychogenic – as distinct from that due to depression or epilepsy) fugue¹⁵⁹⁹ there is sudden, unexpected travel away from home or work, accompanied by inability to recall ones past and confusion about personal identity or the assumption of a new identity. Dissociative identity disorder is the DSM term for MPD (*vide supra*). Twilight¹⁶⁰⁰ (dreamy) states are characterised by disorientation for time and place and impaired short term memory, as if dreaming. Awareness is restricted and attention is poor. Memory may be divided into explicit/episodic and implicit/semantic. The former involves recall of personal experiences identified with the self, e.g. ‘I went shopping yesterday’. The latter involves the execution of routine operations, such as driving a car. There may be different anatomical locations for these two systems, e.g. hippocampal formation and mamillary bodies for episodic memory and basal ganglia and

¹⁵⁹⁷ A sceptic might add that this is similar to a disbeliever in alien abduction being asked to produce contrary evidence.

¹⁵⁹⁸ Pope *et al.* (2007) found no record of cases of dissociative amnesia before 1800 and suggest that it is culture-bound syndrome dating from the nineteenth century.

¹⁵⁹⁹ **Fugue states** can also be associated with cerebral pathology, alcohol and other drugs, malingering, factitious disorder, latak, and amok. Therapy (psychological, amytal, or hypnosis) is aimed at helping the patient to recall what happened leading up to the fugue. Brief fugues often resolve spontaneously whereas chronic cases may prove to beyond help. *Pibloktoq* or ‘running syndrome’ in the Artic is probably a dissociative fugue. Other **culturally determined fugues** may include *possession states* in India, *amok* in Indonesia, *latak* in Malaysia, *bebainan* in Indonesia, and *ataque de nervios* in Latin America.

¹⁶⁰⁰ Unfortunately (David, 2009, p. 5), *twilight states* can refer to one of a number of syndromes ranging from ‘hysterical’ (neurotic) to certain complex partial seizures.

cortex for procedural memory. Leading from these thoughts, it has been suggested, speculatively, that the automaticity of certain dissociative disorders might follow from the separation of self-identification/explicit memory from routine activity/implicit memory. There is fMRI evidence that dissociative disorder is associated with enhanced working memory¹⁶⁰¹. (Elzinga ea, 2007)

Benzodiazepines may worsen dissociation.

The differential diagnosis of *wandering* includes psychogenic fugue (long journey, behaviour normal, amnesia – may be patchy – for episode, +/- assumption of new identity, may last for days), postictal fugue (less purposeful and briefer), depression, acute stress disorder, malingering, dementia, delirium, alcoholic ‘black-out’, head injury, and hypoglycaemia.

Conversion

The term ‘conversion’ assumes transformation of unconscious psychic conflict into a physical symptom. This is difficult ‘prove’ unless there is demonstrable temporal proximity between psychosocial stress and symptom onset or if similar circumstances previously led to ‘conversion’ in the same patient. Conversion disorder is commoner in females (married women in Lahore in one study: Chaudhry ea, 2005) than in males and usually, but not exclusively, commences in late childhood or early adulthood. More severe forms of sexual and/or physical abuse in childhood are reported more often by conversion disorder patients. (Roelfs ea, 2002) Healthy controls feigning a motor difficulty have different cerebral functional scan results to those reported in patients with similar conversion motor symptoms (Spence ea, 2000) but it is difficult at this stage of our knowledge to know what is cause and effect, a problem (in this authors view) with much neuroimaging.

DSM-IV-TR conversion disorder

- Unexplained* symptoms** or deficits affecting voluntary motor or sensory function suggesting a neurological or general medical condition
- Psychological factors judged to be important

*By general medical disorder, drugs, or culturally sanctioned behaviour or experience.

**Cannot simply be pain or sexual functioning.

Culturally sanctioned behaviour or experience would include ladies swooning in years gone by or ‘seizures’ during religious ceremonies. Conversion disorder appears to be more common in rural, less educated, non-Western societies, and may be influenced by lack of opportunity for protest. (Kay & Tasman, 2006, p. 253)

The common assumption that conversion phenomena are more commonly left-sided is not supported by the evidence. (Stone ea, 2002)

Tunnel (tubular) vision

Can only see directly ahead no matter how near or far he focuses (in normal vision horizons widen as eyes focus on objects further away)

Aetiology

Majority - psychological causes

Others - end-stage glaucoma, retinitis pigmentosa, bilateral occipital lobe lesions with macular sparing, migraine

May occur as an aura in TLE

In cases of psychogenic blindness, a vertically striped cylinder is spun in front of the patient. In people with normal vision this will produce involuntary (optokinetic) nystagmus. Visual-evoked responses are another possible test. The therapist might prescribe plain glass in spectacles to allow the patient to save face when his vision is ‘restored’. Cases of so-called functional dysphonia have been said to have difficulty expressing their true feelings! However, one must not miss organic dysphonia¹⁶⁰². In fact, many authorities consider view the majority of ‘functional’ dysphonias as seen today as examples of dystonias and treat

¹⁶⁰¹ Unlike PTSD which is associated with impaired working memory. (Clark ea, 2003)

¹⁶⁰² Recurrent laryngeal palsy, Parkinson’s disease, myasthenia gravis, and disorders of the vocal cords or ventilatory function.

them as such. When a supine patient flexes a thigh to lift the leg there is a downward contralateral leg movement that can be felt by the examiner's hand held under the heel. A patient with psychogenic hemiparesis will show Hoover's sign (lack of downward movement of the 'unaffected' leg when the patient tries to raise the 'paralysed' leg).

Rutter and Hersov (1985) followed up children diagnosed as having conversion hysteria for 4-11 years and almost half were shown to have an organic disorder! Conversion disorder and neurological disorders often coexist. (Fricchione ea, 1999) Suspicion of an underlying somatic disorder should be highest for older patients. Among the many conditions misdiagnosed as hysteria over the years are temporal lobe epilepsy and basal ganglia A-V malformations. In hysterical aphonia there is no vocal cord paralysis (*only* voluntary cord adduction is impaired) and the patient may be able to cough or hum.

Outcome factors in conversion disorder

Better

Mood disorder

Acute onset

Clear precipitation by stress

Early treatment

High IQ

Worse

Personality disorder.

Many conversion disorder patients are subsequently found to have somatisation and other neurotic disorders. (Mace & Trimble, 1996; Şar ea, 2004) Slater's (1965) finding of an excess of neurological disorders on follow up has received little support. (Mace & Trimble, 1996) Nevertheless, the present author has seen a number of acute cases labelled 'hysterical' that turned out to be organic, e.g. subarachnoid haemorrhage, Guillain-Barré syndrome, and cerebral thrombosis. Also, Chaudhry ea (2005) followed up 107 cases (83% female, mean age at start of 23.2 years, 58% married, 73% positive for family history of psychiatric disorder) of conversion disorder in Lahore for 15 years and found that 20% still has conversion disorder, 5% had epilepsy (3 case of complex partial seizures, one case of tonic-clonic seizures), 1 patient had an arteriovenous malformation, 2 cases had vascular headache, 19% had comorbid major depression, and 55% did not fulfil DSM-IV criteria for any disorder. Stone ea (2005) conducted a systematic review of the literature and found that there has been a 4% rate of misdiagnosis of conversion symptoms since 1970. Conversion disorders can be complicated by contractures (e.g. Achilles tendon), pulmonary embolus, and bed sores.

Hysterical overlay

This term is often employed by psychiatrists to infer an inconsistent miscellany of symptoms, signs and behaviours reminiscent of classical hysterical syndromes but here occurring as a reaction to real organic disorder. This phenomenon is more common than pure conversion. Thus a man with known heart disease develops precordial pain with no ECG or enzyme changes or the epileptic has a non-epileptic seizure. It must be realised that organic pain does not always correspond to dermatomes. It is not sufficient to diagnose conversion or dissociation simply on the basis of the non-finding of an organic disorder – positive evidence of a hysterical illness must be sought. Hysteria, in either its conversion or dissociation guises, is rare after 40 years of age, most cases starting before 35 years. Hysteria with onset in middle or old age may be a harbinger of another primary condition.

Hysterical psychosis

Some patients, who often have hysterical personality traits, were said to become abruptly and transiently psychotic when under stress. Hallucinations, when present, were usually visual, vivid and well formed. There could also be delusions, paranoid thinking, bizarre depersonalisation, and grossly unusual behaviour. Immigrants with poor understanding of the local language were typical victims. General care was superior to medication. Hirsch and Hollender (1969) suggested that the modern equivalent is borderline personality disorder with brief psychotic episodes.

Obsessive-compulsive disorder (OCD)

This common disorder¹⁶⁰³ was previously thought to be rare¹⁶⁰⁴, a misconception probably due to the secrecy in which patients often cloud their symptoms, and reliance on hospitalisation rates rather than community rates. The lifetime prevalence in the general population is 1.6-3%¹⁶⁰⁵. In the USA, OCD is said to be the fourth most common psychiatric diagnosis after phobias, substance-related disorders, and major depression. OCD affects equal numbers of males and females or a slight excess of females, although it may come on earlier in males. The mean age of onset is 22 years. Familial cases may have an earlier onset (not all cases are familial), affect an excess of males, and be frequently comorbid with tics¹⁶⁰⁶ and developmental disorders, as well as anxiety, mood and disruptive disorders.¹⁶⁰⁷ OCD patients are common in non-psychiatric clinics, e.g. dermatology.

Various defence mechanisms are said to operate on OCD. With isolation the person is only aware of the affectless idea, the affect and impulse from the idea being repressed. In undoing, a compulsive act is done to prevent or undo consequences imagined to follow thoughts or impulses. Reaction formation involves patterns of behaviour and conscious attitudes exactly opposite to the underlying impulses. Magical thinking means that simply thinking of something causes it to happen (aggressive thoughts frighten the patient). The ambivalent patient harbours love and hate toward the object; this causes conflict that lead to undoing, paralysing doubts and so on.

There is an argument that OCD belongs with the psychoses¹⁶⁰⁸. Certainly one sees OCD patients who harbour notions of near delusional intensity and with barely discernible insight. DSM-IV recognises this and includes the specifier 'with poor insight' and in such cases the additional diagnosis of delusional disorder or psychotic disorder not otherwise specified is allowed.

The patient suffers as a result of preoccupation with thoughts or actions that he knows to be inappropriate. Resistance to such thoughts or actions heightens anxiety. Obsessional themes are very similar across cultures and nations. He may think about harming someone, being contaminated with dirt or bacteria, or his mind may be filled with obscenities. Obsessional thoughts of harming others with knives may prompt the patient to avoid knives. This is not a true phobic avoidance since the fear is not of knives but of the idea of harming someone with them. Doubts may plague him, such as when he constantly checks to see if he really put that cigarette out. Compulsive hand washing is a common example of a compulsive ritual. Their red excoriated hands may be mistaken for allergic dermatitis.

In DSM-IV (and -TR) OCD, and in contradistinction to DSM-III-R, thoughts (praying, counting, repeating words silently) can be either obsessions or compulsions depending on whether they increase anxiety (obsessions) or reduce anxiety (compulsions). In other words what was seen as anxiety provoking (obsessions) now become anxiety reducing (compulsions)! Compulsions are repetitive behaviours (hand washing, ordering, checking, confessing etc.) or mental acts/rituals (praying, counting, repeating words silently, etc.). Obsessions are thoughts, impulses or images. Such images are frequently vivid, morbid and

¹⁶⁰³ Famous probable cases of OCD include Hakuin (1685-1768, Japanese Zen master), Martin Luther (1483-1543), Howard Hughes (1905-76, American millionaire), and John Bunyan (1628-88, author of *Pilgrim's Progress* and *Grace Abounding to the Chief of Sinners*).

¹⁶⁰⁴ Nutt and Ballenger (2005, p. 73 *et seq.*) point out that until 1984 OCD was usually said to affect 0.05% of the population. They also state that not everyone agrees with modern prevalence figures, critics pointing out the scope for exaggeration inherent in the *Diagnostic Interview Schedule* and use of lay people.

¹⁶⁰⁵ **Isolated obsessions (80%) and compulsions (50%)** are common in the general community. For the majority of people such symptoms are often said not to be excessively upsetting, do not take up a large part of their waking hours, and do not significantly interfere with function. However, Fullana *et al.* (2009), using data from the prospective longitudinal Dunedin study of an unselected birth cohort found that both phenomena were common in other psychiatric disorders and in people without mental disorder; in the latter they did cause significant interference; harm-checking was the commonest symptom dimension; anxiety/depression and obsessions (especially aggressive/shameful thoughts) but not compulsions led to help-seeking; and obsessions and compulsions at age 11 were associated with later OCD.

¹⁶⁰⁶ Non-OCD relatives also have an excess of tics and relatives of Tourette patients (even those patients without OCD) are at increased risk for OCD. (Bloch & Leckman, 2008, p. 652)

¹⁶⁰⁷ Some workers (Issler *et al.*, 2010) suggest that OCD comorbid with bipolar disorder may be a different condition from pure BP on the basis that the former may be more severe, have an excess of depressive episodes and residual symptoms, a higher risk for treatment-emergent mania, and anxiety and impulse control burden.

¹⁶⁰⁸ Some experts suggested the term '*obsessive-compulsive psychosis*'. They draw a comparison between this situation and depression with and without psychosis. Nutt and Ballenger (2005, p. 81) suggest that 5-45% and 15% of patients with chronic schizophrenia have OCD symptoms and OCD respectively; many such people are able to tell the difference between internal and external sources of such symptoms; and adding anti-OCD medication may improve OCD symptoms found in people with schizophrenia.

violent, e.g. the man who 'pictures' men's genitalia every time he looks at a (dressed) man, or repeatedly visualises a bad accident or the funeral of a friend. According to DSM-IV, some patients do not have good insight into the excessiveness or unreasonableness of their obsessions and compulsions.

Excessive hoarding, wherein persons cannot throw anything out in case it may sometime prove to be needed, may be due to OCD¹⁶⁰⁹, (Hollander & Simeon, 2003, p. 582) and OCD-related hoarding may be mediated by reduced activity in the cingulate cortex. (Saxena et al, 2004)

Four factors were generated by meta-analysis of symptoms in OCD (Bloch et al, 2008): symmetry, forbidden thoughts, cleaning, and hoarding.

No single theory accounts for the symptomatic heterogeneity of OCD. (Abramowitz et al, 2009)

Cowie (1961) stated that the children of obsessional neurotics have an increased risk of non-specific neuroses but not of obsessional symptoms *per se*. However, Jenike (1989) reported that 20% of the nuclear family have overt obsessive-compulsive neurosis and another 15% have a subclinical form of it. Like OCD cases, their first-degree relatives have deficits in cognitive flexibility and motor inhibition. (Chamberlain et al, 2007) Collection of neuropsychological data at ages 13 and 32 years (Grisham et al, 2009) revealed evidence of premorbid impairment in visuospatial abilities and some executive functions in those who went on to develop OCD.

Blanes and McGuire (1997) suggest that there may be two extreme forms of OCD, a primary type and a neurodevelopmental type. Head-to-head, these two types are characterised respectively by female/male preponderance, late/early age of onset, episodic/chronic course, mild/severe symptoms, frontal/visuospatial neuropsychological impairment, some increase in/excess of soft signs, a good/indifferent treatment response, and a different profile of associated conditions (mood, anxiety and eating disorders v developmental). Nestadt et al (2009) derived three classes of OCD based on comorbidity using multi-level latent class analysis: simplex (major depressive disorder [MDD] is common); tic-related (mainly males; very conscientious; tics are common, mood disorders rare); and affective-related (mainly females; young age at onset; obsessive-compulsive personality features; panic disorder and affective syndromes are common; low conscientiousness).

About 20% of patients have tics as well as OCD. An increased incidence of obsessive-compulsive symptoms occurs in Sydenham's chorea and Tourette syndrome. Monoclonal antibodies identify a B-lymphocyte antigen (D8/17) which is a trait marker for susceptibility to rheumatic fever as a complication of group A streptococcal infection. An excess of D8/17-positive cells have been found in children with Sydenham's chorea, streptococcal infection, and childhood-onset OCD or Tourette syndrome or chronic tic disorders.

PANDAS¹⁶¹⁰

Occurs mostly, but not exclusively, in childhood (Bodner et al, 2001)

Associated with tics and/or OCD related in time to streptococcal infection

ADHD symptoms may be present (Popper et al, 2003, p. 907)

Exacerbations may follow further infections

Anxiety, oppositional defiant disorder, and depression may be present

Often indistinguishable from Tourette disorder

Basal ganglia often normal on neuroimaging (Dale & Heyman, 2002)

There may be a role for anti-basal ganglia antibodies in a 'significant subgroup' of OCD cases (Dale et al, 2005)

Penicillin was ineffective in one pilot study of 37 patients (Garvey et al, 1999) but plasma exchange significantly reduced obsessive-compulsive symptoms in a small (N=10) study. (Perlmutter et al, 1999)

It has been suggested that 'canine acral lick', a form of excessive licking in dogs and cats (often increased by stress) that responds better to antidepressants with a serotonergic profile, might be the canine version of

¹⁶⁰⁹ However, compulsive hoarding is not confined to OCD. (Pertusa et al, 2008) **Causes of hoarding** include OCD, stimulant abuse, autism, anorexia nervosa (uneaten food), Prader-Willi syndrome, Tourette disorder, schizophrenia, schizotypal personality disorder, and anankastic personality disorder. CBT is helpful in the treatment of compulsive hoarding. (Gaston et al, 2009) Compulsive hoarding is common and heritable, at least in females. Non-shared environment also likely plays a part in aetiology. (Iervolino et al, 2009)

¹⁶¹⁰ Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Existence of PANDAS is not universally accepted. (Jankovic & De Leão, 2003)

OCD. Checking by rodents induced by a dopamine agonist may also serve as an OCD model.(Dvorkin ea, 2006)

Genes and OCD

Twin OCD concordance studies: MZ 87%: DZ 47%

Evidence of sequence variation in SCL1A1 gene (encodes neuronal glutamate transporter on chromosome 9p) in OCD (Arnold ea, 2006; Wendland ea, 2009); sequence variation in this gene may explain obsessive-compulsive symptoms induced by atypical antipsychotic drugs.(Kwon ea, 2009)

Association between OLIG2 (gene for oligodendrocyte lineage transcription factor 2 on chromosome 21q)¹⁶¹¹ and OCD in absence of Tourette disorder.(Stewart ea, 2007)

OCD may be due to excessive activity of orbitofrontal-limbic-basal ganglia-thalamic circuitry.

Electrical stimulation research conducted in the early 1970s suggested that the cingulate area might be important in the genesis of compulsive movements. Tests of saccadic function in OCD suggest an abnormality in guiding behaviour on the basis of an internal representation of the task goal, rather than a problem with inhibiting reflexive behaviour; latencies on an antisaccade task are increased.(van der Wee ea, 2006) EEG evidence suggests prefrontal and basal ganglia abnormalities.

Neuroimaging suggests that orbito-fronto-subcortical dysfunction is important in OCD. PET scans has shown increased cerebral blood flow (CBF) in orbitofrontal cortex and dorsal parietal cortex and reduced CBF to the caudate nucleus in drug-free OCD cases. Fractional anisotropy, a measure of water self-diffusion, is bilaterally reduced in anterior cingulate gyrus white matter in OCD.(Szeszko ea, 2005) Increased metabolic rate in the cingulate cortex in OCD on PET has normalised after SSRI treatment, and a reduction in glucose metabolism in the head of the right caudate nucleus has been documented following treatment with either fluoxetine or behaviour therapy. Drug-naïve OCD patients may have a small globus pallidus.(Szeszko ea, 2004) Reduced blood flow to the right inferior frontal cortex has correlated with illness severity. CT scans may show reduced caudate volumes bilaterally – this could lead to inadequate filtering of output from orbitofrontal regions. MRI scans may have longer mean T1 values for frontal white matter and have shown small caudate nuclei. However, caudate volumes have been reported as normal if care is taken to exclude cases with neurological symptoms. There have been reports of increased frontal glucose metabolism and increased blood flow in the medial-frontal cerebral cortex. Female patients undergoing MRI have been reported to have less total white matter and more total cortical volume than controls. Statistical parametric mapping of segmented magnetic resonance images revealed increased regional grey matter density in multiple cortical (incl. left orbitofrontal cortex [OFC]) and subcortical (incl. thalamus) areas and reduced grey matter density in posterior brain areas (e.g. left cuneus and left cerebellum). In OCD following symptom provocation, fMRI shows activation in medial orbitofrontal, lateral frontal, anterior temporal, and insular cortex, as well as in the caudate nucleus, lenticular nucleus, and amygdala, effects that are absent in control subjects. All these findings have been interpreted as indicating heterogeneity in OCD populations. Neuroimaging is still beset with highly technical methodological problems.

Radua and Mataix-Cols (2009) performed a voxel-wise meta-analysis (N = 401 with OCD; 376 healthy controls) and found that OCD is associated with increased regional grey matter volumes in bilateral lenticular nuclei (extending into caudate nuclei) and decreased volumes in bilateral dorsal medial frontal/anterior cingulate gyri; inclusion of severe cases increased the likelihood of finding increased basal ganglia grey matter volumes; and current treatment with antidepressants had no detectable influence on these findings. In a further voxel-wise meta-analysis (Radua ea, 2010) involving 639 patients with anxiety disorders and 737 healthy controls, anxiety disorders (including OCD) were characterised by decreased bilateral gray matter volumes in the dorsomedial frontal/anterior cingulate gyri; OCD was associated with increased bilateral gray matter volumes in the lenticular/caudate nuclei; and patients with other anxiety disorders (chiefly panic and PTSD) had reduced gray matter volumes in the left lenticular nucleus.

¹⁶¹¹ Important in development of myelin-producing cells and highly expressed in brain regions implicated in OCD.

Neuroimaging findings and OCD summarised

2006

Event-related fMRI - behavioural impairments plus aberrant OFC-striatal and dorsal prefrontal activity in OCD on a reversal learning task that addresses function of that circuit

2008

MRI in drug-naive paediatric OCD found more gray matter than in controls in brain areas comprising cortico-striatal-thalamic-cortical circuits

Using DTI to measure fractional anisotropy (FA) of white matter, OCD cases had significantly reduced FA in a large region of right inferior parietal white matter and significantly increased FA in a right medial frontal region – relatives also had significant FA abnormalities in these regions

2009

OCD and major depressive disorder (MDD) show different neural patterns in fronto-striatal and paralimbic areas on fMRI during a self-paced reversal learning task in an event-related design

OCD (on fMRI) is associated with functional alterations of cortico-striatal networks; there is abnormal and heightened functional connectivity of ventrolimbic cortico-striatal regions in OCD

OCD patients may involve other people, including the family, in their rituals. They should be encouraged to a firm but sympathetic stance. The present author has found this to be easier in theory than in practice, so enmeshed may third parties become.

Sixty-seven percent and 25% of OCD patients experience major depression and social phobia respectively at some stage. It is often said that only 15-35% of OCD cases have premorbid obsessional traits, yet Bejerot *ea* (1998) reported that 36% of an OCD sample had obsessive-compulsive personality disorder. Apparent personality disorder, such as dependent or avoidant, may sometimes disappear when OCD is successfully treated. (Ricciardi *ea*, 1992)

In thought stopping the patient either shouts 'STOP' or gives a sharp painful pull to an elastic band around the wrist every time an unwelcome thought enters the head - eventually he may be able to get the same effect from simply thinking about the band. Stress inoculation training consists of distraction, thought-stopping, and self-guided dialogue. Exposure, stress inoculation training, or both treatments combined resulted in equal improvement that was maintained at one year in female assault victims with PTSD. (Foa *ea*, 1999)

Another useful strategy is response prevention, e.g. the compulsive hand-washer has his hands smeared with dirt but is not allowed to wash them. *Exposure and response prevention* (ERP), perhaps best combined with discussion of beliefs and feared consequences, is probably the treatment of choice for OCD but is not readily available,¹⁶¹² although it has been administered effectively over the telephone (Lovell *ea*, 2006) and in group format. (Kearns *ea*, 2010) Its effects are apparently long lasting. Exposure may need to be in imagination if the nature of some obsessions is antisocial, e.g. harming the self or others. Listening over and over again to a recording of oneself giving a commentary of one's thoughts (or simply deliberately dwelling on one's thoughts) may be beneficial for some cases of obsessional rumination, so-called habituation training. There are reports suggesting that cognitive therapy on its own is not effective in OCD. Drugs that have been found to be relatively successful are phenelzine, tranylcypromine (the author has had good results), the SSRIs, and clomipramine¹⁶¹³. The patient does not need to be depressed for the drugs to work. It is stated in the literature that effective drugs tend to be serotonergic, suggesting a possible 5-HT abnormality. There is some basic research evidence to support this contention.¹⁶¹⁴ Desipramine and nortriptyline, which lack serotonin reuptake activity, are not antipanic agents. Certainly SSRIs are probably safer than many other antidepressants. There is almost always relapse on stopping medication. The usual measure of improvement in OCD is a 35-40% reduction from baseline on the *Yale-Brown Obsessive Compulsive Scale* (Y-BOCS) induced by a 10-12 week treatment. Some patients improve further with longer duration of treatment but generally don't achieve complete remission. Augmentation strategies are

¹⁶¹² See De Silva & Rachman (2004) for a readable overview of OCD. ERP may be usefully combined with SSRIs. (Simpson *ea*, 2008)

¹⁶¹³ In order to get optimal results up to 300 mg/day of clomipramine given over at least 10 weeks may be required.

¹⁶¹⁴ E.g., prolactin response to serotonin-releasing d-fenfluramine is blunted in drug-free OCD cases. (Monteleone *ea*, 1997) Also, studies of the 5-HT_{1b} terminal autoreceptor in animals reveal desensitisation following administration of an SSRI. The time frame for this is about eight weeks which is consonant with the time required to produce clinical response in human OCD.

generally disappointing, e.g. pindolol¹⁶¹⁵. Neuroleptics like haloperidol help if there are comorbid tics¹⁶¹⁶ or a family history of tics. SSRIs, especially in high doses, can induce or worsen tics. Clozapine may exacerbate OCD, probably by antagonising 5-HT₂ receptors.

Not all authors are enthusiastic about the benefits derived from exposure therapy and pharmacotherapy of OCD¹⁶¹⁷.

For refractory, disabling cases, limited-site psychosurgery¹⁶¹⁸ offers amelioration with low risk¹⁶¹⁹ whereas repetitive transcranial magnetic stimulation¹⁶²⁰ (rTMS) may be ineffective. (Sachdev ea, 2007) There is preliminary data for the effectiveness of chronic deep-brain stimulation¹⁶²¹ in OCD. (Gabriels ea, 2003) Stimulation of the subthalamic nucleus¹⁶²² reduces Y-BOCS scores but not depression or anxiety in severe OCD and may be associated with operative complications such as infection or haemorrhage. (Mallet ea, 2008)

Skoog and Skoog (1999) described the outcome in 144 Swedish patients after a mean of 47 years from onset of OCD. Eighty-three percent improved, 20% had a complete recovery and subclinical symptoms were found in 28%. Poor outcome correlated with early onset, obsessive-compulsive symptoms, low baseline social functioning, and an early chronic course. So, after several decades, most cases improved, but the majority had clinical or subclinical symptoms. Micali ea (2010) followed up 142 of 222 children¹⁶²³ and adolescents with OCD for over 9 years and found a persistence rate of OCD of 41% and 40% had a psychiatric diagnosis other than OCD; the longer the duration of OCD at assessment the more likely was it to persist; and high baseline psychopathology levels predicted other psychiatric disorders at follow-up. *Obsessional slowness*¹⁶²⁴. These patients form a minority of OCD sufferers. It may relate to covert or overt rituals or indecision with fear of making mistakes or causing disorder, although anxiety levels may be low in practice. Is it a variant of obsessional personality disorder or OCD? Males may outnumber females, there may be a history of prenatal or delivery problems – although most have a history of normal developmental milestones, and there may be a family history of psychiatric disorder in up to half the cases. The pathophysiology may reside in neuronal loops running between the basal ganglia and the frontal lobes. Behaviour therapy is aimed at persuading the patient to speed up and risk making mistakes. This author has found the condition extremely difficult to manage no matter what treatment is used. Attendance at a day centre, often arriving in the afternoon, may be the most that can be achieved.

Depersonalisation

Depersonalisation may occur with anxiety and depression (Baker ea, 2003) or be associated with BZD treatment. Ackner (1954) described the features of this strange experience as ‘always subjective’; the experience being that of ‘internal or external change, characterised by a feeling of strangeness, or unreality ...unpleasant... affect is always involved’. Mellor (1988) excluded the following from the definition: delusional elaboration of the experience; ego boundary disorders of schizophrenia, such as thought insertion; and, loss or attenuation of personal identity. Perhaps most people experience depersonalisation as a transient phenomenon, particularly when fatigued, bored, shocked, in a new or unfamiliar setting, or when deprived of sensory input. Spitzer ea (2006) suggests that there are two different phenomena: compartmentalisation (partial to complete failure to deliberately control processes that we can normally

¹⁶¹⁵ Blocks beta receptors and 5-HT_{1A} receptors to increase serotonin availability in the synaptic cleft.

¹⁶¹⁶ **Tics** (motor or vocal) may be due to failure to inhibit a population of striatal projection neurones which then become overactive leading to disinhibition of the relevant thalamocortical projection neurones. Excess dopamine appears to be involved.

¹⁶¹⁷ E.g. Sheehan(2004) suggests that they deliver about 30% symptom relief.

¹⁶¹⁸ Especially bilateral stereotactic *anterior internal capsulotomy* (destruction of anterior limb of internal capsule – severs thalamo-orbitofrontal fibres) or *anterior cingulotomy* (bilateral severing of anterior supracallosal fibres of anterior cingulate – changes intra-limbic connections).

¹⁶¹⁹ Cf. Irle ea (1998) for German follow up data: frontostriatal lesions did best; ventral striatal lesions associated with later substance dependence, and, 3 cases, those with obsessional personality disorder plus OCD did least well.

¹⁶²⁰ TMS involves using a handheld electrical coil in order to generate a pulsed magnetic field which passes unimpeded through scalp and bone and induces electric fields that depolarise cerebral neurones.

¹⁶²¹ For example, electrical capsular stimulation. Originally used in treatment-resistant Parkinson’s disease, deep brain stimulation works via an electrode in the brain that connects to a pacemaker; continuous electric stimulation instead of a lesion; bleeding and infection are possible.

¹⁶²² Stereotactic MRI, ventriculography and other techniques help to localise the nucleus so that electrodes can be placed correctly.

¹⁶²³ Only 61% (142/222) of these young people and their parents agreed to take part.

¹⁶²⁴ Described by Rachman in 1974.

influence with willpower, such as an inability to bring normally accessible material into awareness) and detachment (subjective feeling of alienation of self or external world).

Depersonalisation disorder as a primary condition is probably rare (grouped with DSM-IV dissociative disorders), although one London *tertiary referral service* dealing with depersonalisation found it in 71% of 204 consecutive referrals (Baker *et al.*, 2003), and consists of a repeated or persistent feeling of being detached from one's mental processes or body that is accompanied by intact reality testing. There is a feeling of unreality or estrangement, mental activity and external life proceed as normal but have a different feel to them, and they stop having any significance for the patient. Patients appear to be in a heightened state of alertness but with a less than expected response to unpleasant stimuli, suggesting a selective inhibition on emotional processing. (Sierra *et al.*, 2002) The disorder tends to affect young people, to have a sudden onset, and the course is often chronic.

In *hemidepersonalisation* there is the feeling that half of the body is unreal or doesn't exist. This lateralised phenomenon is usually right-sided and associated with a focal parietal lesion. In *reduplicative paramnesia* or *double orientation* the patient believes they are in two places simultaneously. *Doubling* refers to the notion that consciousness resides outside the body, perhaps high above the head. Other phenomena include a foreign feel to one's own body, mental behaviour, or behaviour; enlargement or diminution in size of the extremities; etc.

Differential diagnosis

Epilepsy including TLE¹⁶²⁵
 Migraine
 Brain tumour/trauma
 Cerebrovascular disease
 Encephalitis
 General paresis
 Alzheimer's disease
 Huntington's disease
 Spinocerebellar degeneration
 Hypoglycaemia
 Hypoparathyroidism
 Hypothyroidism
 Carbon monoxide poisoning
 Hyperventilation
 Botulism
 Drug effects¹⁶²⁶
 Schizophrenia
 Depression
 Mania
 OCD
 Hysteria
 GAD
 Phobic anxiety
 Schizoid personality disorder (some cases)¹⁶²⁷

Treatment consists of treating any cause of secondary depersonalisation, whereas therapy for the primary disorder is largely untested. Hypnotic induction of transient depersonalisation has been suggested as a way of helping patients understand and gain control over the phenomenon: the patient is encouraged to replace the secondary anxiety reaction with a pleasant feeling of floating or heaviness; and patients may be advised to view their problems on an imaginary screen as a way of 'detaching' them. CBT may help some patients.

¹⁶²⁵ Demonstrated by neurosurgical stimulation of temporal cortex.

¹⁶²⁶ Alcohol, barbiturates, BZDs, scopolamine, clioquinol, β -blockers, cannabis, PCP and related compounds, and hallucinogens.

¹⁶²⁷ Can be severe and persistent.

Fluoxetine was not efficacious for depersonalisation disorder in a placebo-controlled double-blind study. (Simeon et al., 2004)

Generalised anxiety disorder (GAD)

GAD is uncommonly diagnosed by mental health professionals but is common in primary care and in chronic medical populations. (Taylor et al., 2008, p. 440) Despite associated disability, GAD is often missed, ignored, or treated only briefly. The birth of GAD from the soup of anxiety neurosis owes something to Klein's creation of panic disorder, (Klein, 1964) i.e. what remained was renamed as generalised anxiety disorder. (Tyrer & Baldwin, 2006) Human beings need a certain range of anxiety to function adequately, neither too much or too little. 'Double anxiety' refers to the longterm low grade anxious feeling found in GAD patients plus the superimposed briefer periods of increased anxiety that are experienced as part of this syndrome. British soldiers serving in Northern Ireland were found in one prospective study (Lawrenson & Ogden, 2003) to have increased somatic symptoms, anxiety, and social isolation, but no increase in depression ratings. As part of the US National Comorbidity Survey, the one-year prevalence of DSM-III-R GAD was estimated as 4.3% for females and 2% for males. DSM-IV GAD 1-year prevalence for threshold and sub-threshold GAD has been reported as 1.5% and 3.6% respectively (Carter et al., 2001); rates in women and older subjects were 2.7% and 2.2% respectively. The term 'signal anxiety' is sometimes applied to the alerting quality of the sensation, as when it alerts a student to study for an examination. Stein (2003, p. 15) suggests the term 'basic fear circuit' for the brain parts that may be activated in GAD: amygdala (fear conditioning), bed nucleus of stria terminalis¹⁶²⁸ (free-floating anxiety), and hippocampus¹⁶²⁹ (conflict/avoidance). Using fMRI to assess response to facial expression, Blair et al. (2008) found that patients with generalised social phobia had increased responses to fearful as against neutral expressions in the amygdala whereas GAD patients showed excess response to angry expressions in a lateral region of the middle frontal gyrus. Also using fMRI in GAD patients, Nitschke et al. (2009) found heightened and indiscriminate (to both aversive and neutral stimuli) amygdala responses, and of anterior cingulate cortex associations (higher pre-treatment activity associated with greater decreases in anxiety/worry) with treatment response.

Potential medical causes of anxiety¹⁶³⁰

Cardiovascular – angina pectoris¹⁶³¹, congestive cardiac failure, dysrhythmia (paroxysmal atrial tachycardia is terminated by the Valsalva manoeuvre), hypovolaemia, intra-aortic balloon pump, myocardial infarction, syncope, valvular disease, etc

Respiratory – asthma, COPD, pneumonia, pneumothorax, pulmonary oedema or embolus¹⁶³², respirator dependence, etc

Neurological – akathisia, encephalopathy, essential tremor, labyrinthitis, postconcussion syndrome, restless legs syndrome, seizure disorder (*especially* TLE), vertigo, etc

Metabolic – hyperadrenalism, hypocalcaemia, hypoglycaemia, hyperthyroidism, vasomotor symptoms in perimenopausal women (dyspnoea, diaphoresis, feeling hot) or due to tamoxifen

Immunological – anaphylaxis, SLE

Secreting tumours – carcinoid, insulinoma, pheochromocytoma (clonidine reduces catecholamine levels in anxious patients but has no effect on the high catecholamine levels found in pheochromocytoma; anxiety may be more obvious than hypertension)

Peptic ulcer disease

*Drugs*¹⁶³³ – adrenaline, alcohol/barbiturate/BZD withdrawal, amphetamines/cocaine, aminophylline/theophylline, anticholinergics, caffeine, reserpine, hydralazine, isoniazid¹⁶³⁴, cycloserine (although D-cycloserine has been used acutely as an adjunct to behaviour therapy in the treatment of

¹⁶²⁸ A component of the extended amygdala.

¹⁶²⁹ Using PET, Wu et al. (1991) found that GAD cases did not have the usual left-to-right asymmetry in hippocampal metabolism.

¹⁶³⁰ Anxiety derives from Latin *anxietas*, to choke or upset.

¹⁶³¹ Angina can present with palpitations and breathlessness with little chest discomfort.

¹⁶³² Recurrent pulmonary emboli may present as episodic anxiety, dyspnoea and hyperventilation.

¹⁶³³ Including substance use, intoxication or withdrawal as well as bronchodilators, decongestants, over-the-counter drugs, etc.

¹⁶³⁴ **Isoniazid**, an MAOI, can cause many problems, e.g. mania, psychosis, SLE-like syndrome, mixed neuropathy, and encephalopathy (pellagra – isoniazid inhibits tryptophan conversion to niacin). An overdose can cause seizures that respond to pyridoxine. Its mood altering effects were noted during its use as an anti-TB agent. Later it was found to change monoamine concentrations in animal brains, a finding that led to the monoamine theory of depression.

acrophobia [Ressler ea, 2004] and OCD [Wilhelm ea, 2008]), digitalis toxicity, dopamine, ephedrine/pseudoephedrine, calcium channel blockers, L-DOPA, methylphenidate, monosodium glutamate, neuroleptic and other drug-induced akathisia, NSAIDs, nicotinic acid, phenylephrine, phenylpropanolamine, procarbazine, salicylates, steroids, corticotrophin releasing factor*, CCK-4, thyroid hormones, etc. Anxiety can be induced by drugs acting on BZD receptors as inverse agonists (opposite effect to BZDs – β -carboline and diazepam-binding inhibitor), α -2 receptor blockers (e.g. yohimbine), 5-HT agonists (e.g. metachlorophenylpiperazine), caffeine (blocks adenosine receptors), and (see section on panic disorder) sodium lactate. Intravenous lactate, a panic-inducer, reduces plasma GABA levels, and valproate, which increases GABA function by stimulating its synthesis and reducing its degradation, has been reported to block lactate-induced panic. (Belzung ea, 2002) Sodium bicarbonate infusion may be as powerful a panicogen as CO₂ in panic disorder patients, and CO₂ is a common metabolite of both lactate and bicarbonate. CO₂ crosses the blood-brain barrier and induces transient hypercapnia centrally. (Hollander & Simeon, 2003, p. 551)

*CRH increases the startle response via receptors in the bed nucleus of stria terminalis (near amygdala); such enhancement is relatively persistent, whereas fear (short-lived) may be mediated by the amygdala. Startle response to unpredictable aversive stimuli is greater than normal in panic disorder, but not when the stimulus is signalled by a cue. (Grillon ea, 2008) CRH-releasing neurones in the central nucleus of the amygdala project to the bed nucleus.

Problems with DSM-IV-TR GAD: the requirement of 6 months duration is arbitrary and cases of shorter duration may be otherwise indistinguishable; the requirement of ‘excessive worry’ narrows the application of the diagnosis; and the prohibition on diagnosis of panic disorder in the presence of major depression is not in keeping with clinical reality.

Adults with GAD tend to remember their parents as being excessively controlling and overinvolved. (Rapee, 1997) This could instil an excessive fear of the world in the child so that stimuli that would otherwise be met with equanimity are instead reacted to as if they foreshadowed catastrophe. It has been reported that while loss events precede depression, danger events precede anxiety.¹⁶³⁵ Comorbidity between panic disorder, social phobia, and GAD is common. (Yonkers ea, 1996) Chronic GAD often leads to major depressive disorder (MDD). GAD may prolong recovery from treated MDD. Comorbidity of GAD with major depression greatly complicates the clinical picture, with higher levels of suicidal ideation, poorer social function, more other anxiety disorders, eating disorders, and somatoform disorders, than is the case for major depression without GAD. (Zimmerman & Chelminski, 2003) Hamilton (1988) put anxiety neurosis with the affective disorders because of a higher concordance in MZ than in DZ twins, a remittent course, and the response found in some cases to MAOIs. Genetically, GAD and MDD may have a common basis with environment deciding the eventual clinical manifestations. (Kendler ea, 1992) Nutt and Ballenger (2005, p. 220) point out that the actions of antidepressants ‘help to dispel the notion that the anxiety disorders are but a variant of depression’, e.g. effective doses differ, time of onset of full therapeutic effect is longer for anxiety, and noradrenergic drugs work for depression but not for OCD. Also, in a 10-year prospective study, Beesdo ea (2010) found that anxiety and depressive disorders differ regarding risk constellations and patterns over time; they concluded that GAD is a heterogeneous condition that resembles other anxiety disorders more than depressive conditions; however, GAD may differ from depression and other anxiety disorders with regard to family climate (dysfunction and distress) and personality profiles (high reward dependence and poor childhood attachment experiences).

Relative to normal mice, heterozygous GABA-A γ 2 subunit knockout mice are anxious, hypervigilant and less sensitive to benzodiazepines, have decreased brain GABA-A ligand binding. (Tyrer & Baldwin, 2006) Goldberg (2008) has reviewed the tension between those experts who see GAD and MDD, as currently defined, as separate disorders and those who view them as the same condition.

From a cognitive viewpoint, anxious patients have an emotional bias in responding to potentially threatening stimuli, a tendency to interpret situations as being unrealistically dangerous or risky (although

¹⁶³⁵ Whether these are independent events or interpretations based on mental state is difficult to say. Interestingly, it has been reported that loss rather than danger events precede panic disorder.

they usually retain insight into the excessive and inappropriate nature of their worries), enhanced recall for memories associated with threatening situations or past anxiety states, and automatic thoughts associated with themes of danger, threat, uncontrollability (and dislike of unpredictability), or anticipated incompetence. There are high frequencies of negative self-statements, misinterpretations of bodily stimuli, and overestimates of future misfortune.

Some authorities disagree with the DSM stress on worrying in the definition of GAD, instead focusing on tension, psychic and somatic, which in turn may lead to (the avoidance behaviour of) worry¹⁶³⁶. (Rickels & Rynn, 2001)

Somatic concomitants of anxiety are mediated by the autonomic nervous system. Resting blood pressure, skin conductance (expressed as the GSR: galvanic skin response), heart rate, and respiration are not consistently different from the healthy population. (Taylor ea, 2008, p. 441) However, the association of GAD with stable coronary heart disease is associated with an increased risk of cardiovascular events. (Martens ea, 2010)

The responses of the EMG and the autonomic nervous system to repeated auditory stimuli show that they habituate more slowly in anxious people than in normals. Anxious patients have difficulty inspiring whilst asthmatics have problems expiring. The increase in lactate after exercise may be greater in anxiety states than in normals. When attempting to distinguish anxiety from paroxysmal tachycardia one should find out from the patient if awareness of feelings of anxiety or of rapid heart action came first.

Benzodiazepines reduce the central manifestations of anxiety. Beta-adrenoreceptor blockers, such as propranolol (Inderal), reduce the peripheral, autonomic effects. However, they do not reduce palmar sweating because the sympathetic nerve supply to palmar sweat glands is cholinergic. Beta-2 agonists such as salbutamol and terbutaline may cause tremor and a feeling of tension in the musculature. CCK-4-induced anxiety is associated with increased cerebral¹⁶³⁷ and extracerebral blood flow; the increased blood flow may commence in the hypothalamus and later involve the claustrum and insula. (Liddle, 2001, p. 175) DeBellis ea (2000), using MRI, found that children with GAD had bigger right and total amygdala volumes in comparison to healthy controls.

The 5-HT₂ agonist m-chlorophenylpiperazine (m-CPP) may increase anxiety and anger in GAD but not in healthy controls. (Germine ea, 1992)

Psychological anxiety symptoms include apprehensiveness, irritability, malaise, dizziness, depersonalisation/derealisation, and intermittent low mood. (Marks, 1991) *Metaworry*, or worrying about worry itself, increases worrying in GAD. Insomnia consists of the initial and middle (interrupted) variety. Ideas of reference may occur in some patients, but insight is retained. The somatic symptoms of anxiety include palpitations, breathlessness, precordial pain, paraesthesiae, sweating, cold palms, flushing, tremor, fatigue, dry mouth,¹⁶³⁸ and frequency of micturition. Increased muscle tone accounts for the tremor. Morning vomiting may be associated with alcohol, pregnancy, or anxiety. Despite persistent vomiting, if there is no weight loss a psychosocial cause is most likely. However, beware of vomiting that relieves pain: outrule peptic ulceration. Secondary depression and alcohol abuse are common in psychiatric clinic attenders.

The anxiety reaction resembles the 'fight or flight' reaction in animals.¹⁶³⁹ The bowels and bladder may empty, as every soldier finds out to his horror and disgust on the battlefield. Peripheral changes cause an increase in anxiety, so leading to a vicious cycle of events. Anxious people are slow to adapt to change. EEG alpha waves decrease as anxiety levels escalate.

The middle-aged person who develops an anxiety state for the first time may be depressed or harbouring an organic disease, e.g. carcinoma. Psoriasis is made worse by such factors as anxiety or lithium. Fungal infections of the feet, axillae and perineal regions are common in anxiety states (possibly related to hyperhidrosis).

Management of anxiety

¹⁶³⁶ Patients act as if worrying will prevent an undesired outcome. **Worry**, in fact, impedes processing of emotional material and blocks extinction.

¹⁶³⁷ Anterior cingulate gyrus, claustrum, insula, amygdala, and vermis of cerebellum.

¹⁶³⁸ Xerostomia.

¹⁶³⁹ Hans Selye of Montreal did much of the early work in this area.

Relaxation exercises¹⁶⁴⁰
 Breathing exercises to control hyperventilation
 Counselling (Donnan ea, 1990)
 Supportive psychotherapy
 Behaviour therapy (systematic desensitisation)
 Cognitive therapy (even brief therapy may help)
 Anxiety management groups
 Other forms of psychotherapy
 Transcendental meditation (TM)
 Autogenic training (relax by silently repeating calming, peaceful phrases)
 Yoga
 Biofeedback
 BZDs (in the short term, although a minority need BZDs in the long term¹⁶⁴¹; possibly better than buspirone for somatic symptoms and insomnia [Huppert & Rynn, 2004])
 Buspirone¹⁶⁴² (possibly more effective for cognitive than somatic symptoms, and ineffective in panic disorder [Sheehan ea, 1993])
 Antihistamines (e.g. hydroxyzine: very sedative and questionable efficacy as anxiolytic drugs: Lader, 1994; Leonard, 2003, p. 236) – however they are relatively safe (hypotension can be problematic) and may prove useful where respiratory depression has to be avoided
 Antidepressants¹⁶⁴³ (in the longer term, e.g. imipramine,¹⁶⁴⁴ duloxetine (Nicolini ea, 2009), or the SSRIs¹⁶⁴⁵ – as with buspirone¹⁶⁴⁶, the anxiolytic effect may be delayed for a few weeks; escitalopram 10 mg/day [Baldwin ea, 2006]; venlafaxine has been recommended for GAD and its extended release form offers advantages)(Liebowitz ea, 2005; Nicolini ea, 2009)
 Neuroleptics in small doses are useful and justified in persistent anxiety in dependence-prone patients or in aggressive people who may be disinhibited by anxiolytics
 Abecarnil (novel anxiolytic beta-carboline: said to have an onset of action in about one week¹⁶⁴⁷ and to be unaccompanied by either rebound or withdrawal symptoms – it may not be as useful for anxiety as BZDs or buspirone
 Pregabalin (Lyrica; non-BZD relative of GABA): used for anxiety disorders, especially GAD,(Rickels ea, 2005; Montgomery ea, 2008) diabetic neuropathy, and epilepsy, and perhaps fibromyalgia as well; binds to α -2-lambda subunit of voltage-gated calcium channels and has other downstream effects
 Kava reduces anxiety but may cause liver problems (Gale & Davidson, 2007) and parkinsonism (Lees ea, 2009)

The key element in virtually every successful non-drug intervention in the anxiety disorders as a group is exposure to the fear-producing stimulus or situation. Unfortunately, specific psychotherapies are rarely available outside specialist centres.(Cowley & Roy-Byrne, 1997) In anxiety management training, two stages can be discerned: verbal cues and mental imagery are used to arouse anxiety; and the patient is then trained to reduce anxiety using relaxation, distraction, and reassuring self-statements. Changes in life style may be required. Anxious people may turn to alcohol for fast relief.

Some authors state that most cases of anxiety disorder resolve after a few months, whereas others find it to be a chronic illness. If the patient is still anxious at 6 months then he is likely to be unchanged at 3 years. Increases in mortality rates from suicide and secondary to alcohol and smoking have been

¹⁶⁴⁰ E.g. Jacobson's Progressive Relaxation.(Jacobson, 1938)

¹⁶⁴¹ GAD is a chronic disorder (many authorities view GAD as a problem of temperament, often becoming more pronounced with increasing age) so short-term (< 4 weeks) may not suffice and long-term, intermittent treatment may be indicated.

¹⁶⁴² Buspar was withdrawn, December 2009.

¹⁶⁴³ Continue antidepressants for at least 6-8 months and probably for longer in cases if there is some initial response as partial responders may convert late to complete responders.(Nutt & Ballenger, 2005, p. 31)

¹⁶⁴⁴ Withdrawn from market.

¹⁶⁴⁵ Antidepressants and buspirone may be more effective for psychological symptoms and the BZDs better for physical complaints.(Kelsey ea, 2006, p. 149) However, duloxetine and extended-release venlafaxine may tackle both types of symptoms.(Nicolini ea, 2009)

¹⁶⁴⁶ Buspar was withdrawn, December 2009.

¹⁶⁴⁷ It combines with the BZD-GABA complex, being a partial agonist and full agonist at different sites.

recorded.(Allgulander, 1994) In some ways, pure GAD is at least as disabling in terms of quality of life as is pure major depressive disorder.(Wittchen ea, 2000)

Panic disorder

The essential elements of DSM-IV-TR panic disorder are *recurrent* panic attacks *and* persistent *concern* about panic attacks or *behaviour* that is changed because of panic attacks. The notion of panic¹⁶⁴⁸ attacks constituting a distinct form of anxiety disorder (so-called 'panic disorder') dates to Klein (1964) who noted that these attacks responded to imipramine whilst the background of generalised anxiety did not. He did not explain how agoraphobia can occur without panic disorder ('more common than was once thought' [in the US]; Schatzberg ea, 2005, p. 23; Bienvenu ea, 2006) and his failure to find efficacy for benzodiazepines in panic disorder was due to his employment of low doses. It should be noted that not every expert agrees with the removal of panic disorder from the general body of anxiety.(e.g. compare Basoglu ea, 1992 with O'Rourke ea, 1996) Others point out that the diagnosis of panic disorder is not stable, many cases developing alcohol abuse, agoraphobia and depressive illness.(Casey & Craven, 1999) Research conducted by Goisman ea (1995) suggests that agoraphobia without a history of panic disorder, uncomplicated panic disorder, and panic disorder with agoraphobia are really part of a continuum, rather than discrete diagnoses. Females with panic disorder are more likely to be agoraphobic and to have comorbid depression.(Nutt ea, 2002, pp. 17-18) The notion that all panic attacks in panic disorder are uncued is unlikely to be valid.(Welch ea, 2008, p. 542)

In general, about one-half of all cases of panic disorder experience at least one episode of depression at some point during life, although reported figures vary widely. Nevertheless, the high rates of comorbidity do not seem explicable by chance. There are many postulated reasons for this comorbidity: co-occurrence of two common disorders, overlapping diagnostic criteria, those cases with both groups of symptoms have a unique disorder, panic leads to depression, etc. Compared to the relative of someone who is simply depressed, the relative of a patient who has panic plus depression is at greater risk of developing affective, anxiety, or alcohol abuse problems, although the former relative is also at increased risk for developing anxiety (and panic) disorder.

Female cases outnumber male sufferers in all countries. The commonest affected age group for the disorder is 25-34 years. As a generalisation, 1 in 10 people has occasional panic attacks and 2% of people have panic disorder.¹⁶⁴⁹ Infrequent panic attacks can be associated with considerable disability.(Katerndahl & Realini, 1997) Also, agoraphobic avoidance and apprehensiveness may be functional more impairing than the frequency of panic attacks.(Telch ea, 1995)

Panic disorder

DSM-III-R one-year prevalence - 32/1000 women, 13/1000 men

Low lifetime prevalence of 14/1000 reported from Edmonton, Alberta

Higher figure of 29/1000 from Florence, Italy

Taiwan, which reports low rates of most psychiatric disorders - lifetime prevalence of only 4/1000

Baltimore Epidemiologic Catchment Area Study (Eaton ea, 1998) - annual incidence 1.43/1000/year; incidence was greater in females and declined with age; one-third of new cases arose without agoraphobia, but half had anxiety of some sort for many years before meeting criteria for panic disorder; and cases with agoraphobia had milder onsets but slower recoveries than those without agoraphobia

In fact, ECA study showed almost half of patients with one anxiety disorder experienced another anxiety disorder during their lives (Nutt ea, 2002, p. 19)

In various studies, 7.9%-41% of relatives of patients with panic disorder have panic disorder at some point in their lives, compared with 0.8%-8% in the families of controls

Sore neck (fear that a blood vessel will burst from blood pressure or 'wind') affects Cambodians and *wind overload* affects Vietnamese

¹⁶⁴⁸ The word panic is derived from the naughty god Pan who frightened Greeks who ventured into woodland.

¹⁶⁴⁹ **National Comorbidity Survey Replication** (NCS-R: Kessler ea, 2005) found lifetime prevalence rates of 4.7% for panic disorder and 1.4% for agoraphobia without panic. American household survey(Kessler ea, 2006) using CIDI reported the following lifetime prevalence estimates: panic attacks (PA) only = 22.5%, PA + agoraphobia without panic disorder (pd) = 0.8%, pd without agoraphobia = 3.7%, and pd + agoraphobia = 1.1%.

There is some conflict in studies looking at the incidence of panic disorder in African Americans; panic disorder may be complicated by *isolated sleep paralysis* (Bell ea, 1984)
Ataque de nervios is found in Latino groups and resembles panic disorder except that patients show greater loss of emotional control (e.g. by screaming or crying uncontrollably); about a third meeting DSM-IV criteria for panic attack and somewhat less meet criteria for panic disorder (APA, 2009, p. 44)

According to Nutt ea,(2002, p. 43) twin studies have given mixed results and linkage studies have been negative, although Woo ea (2002) suggest that vulnerability to panic disorder, and a poorer response to treatment, may be associated in some cases with possession of the LL COMT genotype.
 Collier (2002) reviewed the interesting possibility that a slightly longer arm of chromosome 15 may cause panic disorder. He points out that joint laxity¹⁶⁵⁰ is more likely in panic disorder. Fluorescent *in situ* hybridisation (FISH) provided evidence of genomic duplication¹⁶⁵¹ in chromosome 15 that is present in only some cells (mosaicism). Unlike other human disease-causing duplications that arise during meiosis, DUP25 appears to arise during mitosis. Possible candidate genes in the affected gene include those for three nicotinic acid receptors and the neurotrophin-3 receptor¹⁶⁵².

Based on dreams and 'screen memories', a connection with separation anxiety has been proposed. There is certainly some evidence to support this claim.(Lipsitz ea, 1994) Nevertheless, such research depends on the accuracy of recollection of parenting styles by grown ups. Aschenbrand ea (2003), based on a 7-year longitudinal study, point out that separation anxiety disorder is not synonymous with panic in children and that it does not necessarily continue as adult panic disorder, although they acknowledge that separation anxiety disorder is more common in the children of people with panic disorder. Nutt ea (2002, p. 46) list parental separation, critical or overprotective parenting, sexual and/or physical abuse, as well as separation anxiety, as childhood risk factors for panic disorder. Nevertheless, the separate diagnosis of separation anxiety disorder persisting into adulthood has been neglected¹⁶⁵³ and such a diagnosis in a parent of a child with separation anxiety disorder may be commonplace.(Popper ea, 2003, p. 931) In a multivariate twin study, Battaglia ea (2009) found that shared genes appeared to explain the continuity of separation of anxiety into adult panic disorder (and the increased sensitivity of both conditions to CO2) but that parental loss in childhood also has a role to play. Propranolol, haloperidol, and perhaps risperidone more than olanzapine may induce separation anxiety in children whilst the medication is taken.(Popper ea, 2003, p. 932)

As reported in depression,(Sørensen & Bech, 2006, p. 14) there may be decreased beat-to-beat variation (reduced cardiac rate variability) in panic disorder patients as a result of decreased and increased vagal and sympathetic tone respectively (Kawachi ea, 1995); such reduced variability being worsened by isoproterenol and lactate and diminished (i.e. increased heart rate variability) by anti-panic treatments such as paroxetine.(Tucker ea, 1997) However, the reduced heart rate variability found in depression may be due mainly to antidepressants, including TCAs and SSRIs.(Licht ea, 2008)

It has also been suggested (Klein, 1993) that panic disorder may be due to a hypersensitive CO2 chemoreceptor system coupled with cognitive distress, the brain reacting as if its owner is being suffocated¹⁶⁵⁴; this 'anxiety sensitivity' may very well be inherited¹⁶⁵⁵. There is some evidence from proton MRS to suggest that hyperventilation may lead to disproportionate increases in brain lactate in panic disorder and that brain lactate is already increased before a lactate infusion in panic patients who respond to lactate compared to those who fail to respond.(e.g. Dager ea, 1995) The same workers later found greater brain lactate increases in panic disorder patients compared to controls after IV lactate infusion. Bellodi ea (1998) found a significantly higher concordance for 35% CO2-induced panic attacks among MZ (55.6%)

¹⁶⁵⁰ ? related to lysyl oxidase.

¹⁶⁵¹ Termed DUP25 – found in 7% of normal population and 68-70% of panic disorder cases.

¹⁶⁵² The latter is the only neurotrophin receptor expressed in the locus coeruleus.

¹⁶⁵³ Shear ea (2006) found that lifetime prevalence for child and adult separation anxiety disorder were 4.1% and 6.6% respectively; one-third of childhood cases persisted into adulthood, but 77.5% developed the disorder as adults. Most adult cases are untreated specifically for this disorder. The patient may be anxious about the health of a loved one, become anxious when the partner goes to work, be unable to sleep when a partner is away on a business trip, telephone him constantly, call personally to a partner's place of work when he cannot be raised by 'phone, etc.

¹⁶⁵⁴ At the opposite extreme in the rare disorder, with attendant risk of death during sleep, *Ondine's curse*. Here we have a hyposensitive suffocation alarm.

¹⁶⁵⁵ However, earlier traumatic suffocation (e.g. almost drowning) is another possibility.(Bouwer & Stein, 1997)

than DZ (12.5%) twins, which favours a genetic predisposition to panic attacks. Miller *et al.* (2000) reported no change in resting anxiety levels in panic disorder or normal controls after tryptophan depletion. Only the patient group developed panic after receiving 5% CO₂. Kent *et al.* (2001) found that both panic disorder and premenstrual dysphoric disorder patients were very susceptible to CO₂-induced panic attacks, while depressives were immune to this procedure. They concluded that CO₂-induced panic had similar intensity regardless of diagnosis. Pine *et al.* (2005) found no support for CO₂ hypersensitivity as a familial marker for panic disorder in children and adolescents but they did replicate a link between childhood anxiety disorders and CO₂ sensitivity, i.e. CO₂ was a marker of anxiety not a familial risk factor for panic disorder. A centrally acting muscarinic antagonist like biperiden (Akineton) may block CO₂-induced panic attacks. (Battaglia *et al.*, 2001) Kent *et al.* (2005) used PET and doxapram (an acute respiratory stimulant) challenge and found that low perfusion of orbitofrontal cortex was associated with increased anxiety. Electrical stimulation of the dorsal periaqueductal grey matter during neurosurgery causes neurovegetative changes and feeling of terror similar to panic attacks, and PET during lactate-induced panic showed activation of the midbrain tectum, part of which includes the dorsal periaqueductal grey matter. (see Graeff & Zangrossi, 2002)

Flumazenil, a BZD antagonist, caused panic in panic disorder patients but not in well people in one study (Nutt *et al.*, 1990) but it failed to induce panic in another study. (Strohle *et al.*, 1999) BZDs are less effective in panic disorder patients than under other circumstances, large doses being required. There is MRS evidence of reduced cortical GABA in panic disorder patients but not in well people. This may be a trait phenomenon. (Goddard *et al.*, 2004) Using PET and flumazenil tagged with carbon 11, Hasler *et al.* (2008) a particularly strong reduction in BZD receptor binding potential in the dorsal anterolateral prefrontal cortex in panic disorder patients never treated with BZDs and also a particularly strong increase in BZD receptor binding potential in the hippocampus/parahippocampal gyrus.

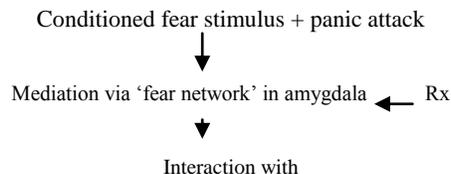
At low doses, the 5-HT₂ agonist m-chlorophenylpiperazine (m-CPP) induces panic in panic disorder patients but not in healthy people.

The CSF content of cholecystokinin in panic disorder cases has been found to be lower than expected. Nocturnal production of melatonin, a derivative of serotonin, may be increased in panic patients. CO₂ inhalation and sodium lactate (both increase cerebral blood flow), CCK4 (cholecystokinin tetrapeptide¹⁶⁵⁶), or isoproterenol (beta-antagonist) can precipitate panic attacks, although whether they are syndrome specific¹⁶⁵⁷ is subject to ongoing research. Transcranial Doppler ultrasonography has shown reduced basilar artery blood flow during hyperventilation in panic disorder patients that may respond to nimodipine, a centrally active calcium channel-blocking agent. Reduced peripheral beta-adrenoreceptor density and decreased cAMP responsivity normalising with adinazolam treatment has been reported in panic disorder patients who also have agoraphobia. (Maddock *et al.*, 1993) It was shown in the 1980s that panic patients actually increased their heart rates after an infusion of the β -stimulant isoproterenol. There is some evidence for cholinergic hyperactivity in panic disorder: augmented growth hormone response to pyridostigmine challenge.

Hypotheses concerning the genesis of panic disorder are outlined in the diagram. According to Gorman *et al.* (2000) heritable factors and stressful life events (especially if experienced early in life) may be responsible for the onset of panic disorder. Drug treatment (especially if serotonergic) might desensitise the 'fear network' and psychosocial treatments might reduce contextual fear and cognitive misattribution at the level of the prefrontal cortex and hippocampus.

Some theories regarding the origin of panic disorder.

After Gorman *et al.* (2000):*



¹⁶⁵⁶ Pentagastrin (synthetic CCK-4 analogue) induces panic in normals and anxiety sufferers. (Uhde & Singareddy, 2002)

¹⁶⁵⁷ **Anxiogenic probes** (lactate, CO₂, pentagastrin, etc) produce effects in social anxiety disorder that lie between normals and panic disorder. (e.g. McCann *et al.*, 1997)



Hippocampus + prefrontal cortex + brainstem ← behaviour Tx

After Klein(1981):

Spontaneous unprovoked panic attack
leads to
 Cued panic attacks
leads to
 Anticipatory anxiety
leads to
 Agoraphobia

After McNally and Lorenz(1987):

It is not misinterpretation of somatic sensations that causes panic, but rather the belief that the sensations *per se* are dangerous.

After Wolpe and Rowan(1988):

Anxiety
leads to
 Hyperventilation that causes dizziness + paraesthesiae
which, on repetition leads to
 Conditioned stimuli that can provoke panic attacks

After Clark(1988):**

Interoceptive or exteroceptive stimulus
leads to
 Perception of threat
leads to
 Apprehensiveness
leads to
 Somatic sensations
leads to
 Misinterpretation of sensations leading to panic attack
leads to perception of threat and vicious cycle repeats itself

After Klein(1993):

Panic disorder is due to excessively sensitive brainstem suffocation alarm

After Shear ea(1993):

Innate irritability + unsettling parental behaviour
leads to
 Unresolved dependence/independence issues
leads to
 Excess negative affect
leads to
 Increased biological sensitivity
if added to
 Significant stressor
leads to
 Loss of sense of being safe and being in control
if added to
 Strong negative affect
leads to
 First panic attack

*Based on animal studies. **Vulnerability involves a tendency to think too much about first panic experience with subsequent hypervigilance.

Faravelli ea (1992) found that 78% of panic disorder with agoraphobia patients had their first panic attack in phobogenic situations as against only 20% of panic disorder without agoraphobia cases. Phobic avoidance is common. These patients are often seen by a variety of specialists before being sent to a mental health expert, e.g. an urologist because of urinary frequency, a cardiologist because of chest pain, (Bass & Mayou, 2002) or a neurologist because panic may mimic epilepsy, especially complex partial seizures. (In fact, to make life complicated, there have been several reports of right focal temporal lesions presenting with panic attacks.) Typical features of partial seizures are short attacks (1-2 mins.), witnessed motor automatisms (e.g. regular swallowing, chewing, or clothes plucking), over 45 years of age at onset, a history of febrile convulsions, and lack of response to conventional antipanic treatments. (Thompson ea, 2000) Panic attacks can rarely be attributed to hypoglycaemia unless there are other pointers to this diagnosis.

There is usually a high level of anticipatory anxiety between attacks, i.e. fear of having another panic episode. The following symptoms were reported in over 80% of cases in a report by Noyes *et al.* (1987): fearfulness/worry/apprehension, nervousness, palpitations, muscle aches/tension, trembling/shaking, dizziness/imbalance/faintness/lightheadedness, fear of dying/going crazy, and hot/cold sensations. DSM-IV-TR defines a panic attack as a discrete period of intense fear or discomfort, in which at least 4 of the symptoms listed in the table develop abruptly and reach a peak within 10 minutes. DSM-IV limits the use of a GAD diagnosis by diagnosing panic disorder after just one panic attack. (Schatzberg *et al.*, 2005, p. 24)

DSM-IV-TR and panic

(a) panic attack

- | | | |
|-------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------|
| 1. palpitations, pounding heart, or tachycardia | 6. chest pain or discomfort | 10. fear of losing control/going crazy |
| 2. sweating | 7. nausea/abdominal distress | 11. fear of dying |
| 3. trembling/shaking | 8. feeling dizzy, unsteady, light-headed, or faint | 12. paraesthesiae (numbness or tingling) |
| 4. sensations of dyspnoea/smothering | 9. derealisation (feelings of unreality) or depersonalisation (being detached from oneself) | 13. chills or hot flushes |
| 5. feeling of choking | | |

(b) panic disorder

1. recurrent, unexpected panic attacks
2. at least 1 attack followed by at least 1 month of persistent concern about having another attack/worried about effects of attacks (heart attack, loss of control, going mad, etc)/or significant behavioural change related to the attacks
3. with/without agoraphobia
4. Not due to substances/medical disorders
5. Not better accounted for by another mental disorder, e.g. social phobia

Note: Hyperventilation causes hypocapnia and alkalosis with reduced cerebral blood flow. Hence the patient feels dizzy, unreal, changed, or detached.

Behavioural approaches (gradual exposure to a hierarchy of feared situations) can be effective but tend to be distressing to the extent of the patient opting out of the programme. Exposure to panic cues can be brought about by various exercises, e.g. breathing through a straw, running in place, or spinning in a swivel chair. Simple relaxation exercises and respiratory training often fail because the surges of anxiety may come on too quickly to allow conscious control mechanisms to operate; the patient must practice these techniques between episodes so as to become convinced that they can perform them correctly.

Cognitive-behaviour therapy (CBT) is effective (if available: APA, 2002, p. 672, 2009, p. 9; Nutt *et al.*, 2002, pp. 67 & 88), and may have more persistent effects than drugs. CBT may be added at any point in the ongoing management of panic disorder. (Welch *et al.*, 2008, p. 547) Panic symptoms can be induced by exercise or hyperventilation for the purpose of analysis and reflection. The patient then has to learn not to assign symptoms to catastrophe such as impending death, loss of control, or madness, but instead to reassign them to a cause of lesser significance. *Interoceptive exposure* refers to the gradual exposure of a patient to feared physical sensations, repeated exposure leading in turn to habituation. Cognitive restructuring is combined with interoceptive exposure. Safety behaviours (e.g. carrying a mobile 'phone or tranquillisers as a 'crutch') may reduce the effectiveness of exposure therapy. CBT has been shown to be at least as good as high-dose imipramine. It has been claimed that some patients who remitted after CBT have lost their vulnerability to lactate-induced panic attacks. CBT helps panic disorder patients to wean off BZDs. Group CBT is effective for panic disorder. (APA, 2009, p. 29)

There is some concern (APA, 2009, p. 27) that the combination of medication plus CBT may interfere with maintenance of treatment response following treatment withdrawal.

Family and insight-orientated treatments (Milrod *et al.*, 2007) have their place, e.g. for family complications or to convince someone of the need for drug therapy. *Panic-focused psychodynamic psychotherapy* (Milrod *et al.*, 1997) has a slender evidence base (Milrod *et al.*, 2007) than that for CBT. It is given individually and is time-limited, i.e. twice a week over twelve weeks. The theory involves assuming difficulty withdrawing from important attachment figures and poor perceived autonomy. The latter may underlie agoraphobic

avoidance behaviour. The transference is used to promote change and to encourage confrontation of the emotional significance of panic symptoms. Symptoms may transiently worsen as material surfaces. Aims include increased autonomy, relief of symptoms, and better functioning.

Psychodynamic approaches are often used together with medication. Supportive psychotherapy and eye movement desensitisation and reprocessing (EMDR) are unhelpful. Relaxation therapy is less effective than CBT.(Siev & Chambless, 2007)

Caffeine¹⁶⁵⁸ and nicotine should be avoided. Comorbid agoraphobia and depression need attention. The present author's practice is to advise abstinence from alcohol: some patients self-medicate for panic with alcohol, others only panic because they are drinking, and anyway one is unlikely to get anywhere as long as alcohol contaminates the clinical picture. Stimulants, cannabis, and sympathomimetics (as in nasal decongestants) can precipitate panic attacks at any age. Regular aerobic exercise, like running, is superior to placebo but less effective than clomipramine.(Broocks ea, 1998)

NICE suggests that benzodiazepines (BZDs) be avoided in the treatment of panic disorder. Alprazolam (originally used in doses up to 4-10 mgs per day in 4 or 5 doses – modern recommendations are 2-4 mgs; O'Shea, 1989 – a therapeutic window of 20-40 nanograms per ml. has been suggested) and imipramine have been advocated for the treatment of panic disorder. Not all studies find an effect for alprazolam that is stronger than placebo and there were doubts as to whether any gains from alprazolam last,(Marks ea, 1993) although some authors reported longterm improvement with alprazolam.(Nutt ea, 2002, p. 75) Briggs ea (1993) found that patients with prominent respiratory symptoms tended to have more spontaneous attacks and to respond to imipramine, while those without prominent respiratory symptoms had more situational attacks and responded more to alprazolam. Boyer's (1995) meta-analysis showed SSRIs to be superior to alprazolam and imipramine for panic disorder.

Clonazepam, now generally seen as the BZD of first choice for panic disorder, has a longer elimination half-life than alprazolam. This allows more stable drug levels and twice daily dosing. Start with 0.25-0.5 mgs/day and increase to 1-2 mgs/day in two divided doses, although even higher doses may be needed for complete relief. There may be fewer problems associated with stopping clonazepam than alprazolam. Patients may be switched from alprazolam to clonazepam by dividing the total daily dose of alprazolam in milligrams to get that for clonazepam.

Lorazepam should be started at 1.5-2.0 mg/day and increased to 4-8 mgs/day as needed. The daily dose should be split into 3 or 4 doses.

What probably matters for efficacy is not so much which BZD that is used but rather that the dose be sufficient, e.g. 40 mg of diazepam v 4 mg of alprazolam.(Noyes ea, 1996) Also, BZDs should be used on a regular schedule than on an as needed (prn) basis.(APA, 2009, p. 30) There is a high relapse rate after stopping BZDs, and probably after stopping any effective drug therapy. Therefore drug treatment may need to be continued for a long time.¹⁶⁵⁹ Cessation of BZDs needs to be done very slowly, over 2-4 months, and at a rate of 10% reduction in dose per week at the most. Patients treated with BZDs for panic disorder have not tended to show tolerance or escalation of doses.(Nutt ea, 2002, p. 77)

Beta-blockers are not effective in panic disorder. Clonidine may reduce symptoms at the start of treatment in some cases but its effects wanes over some weeks¹⁶⁶⁰. Bupropion and ritanserin (5-HT receptor agonist) lack efficacy in panic disorder. Indeed, bupropion may be anxiogenic.(APA, 2002, p. 492) Valproate can be effective.(Lum ea, 1990) SSRIs¹⁶⁶¹, MAOIs¹⁶⁶² (including RIMAs), TCAs¹⁶⁶³, venlafaxine (in low dosage it may be a pure SSRI),(Bradwejn ea, 2005) nefazodone (withdrawn from market), and mirtazepine, but not buspirone,(Deakin ea, 2001) appear to be effective antipanic agents. Data on the newer agents is not as strong as for SSRIs and TCAs. CCK-B receptor antagonists have so far proved disappointing. There is some preliminary evidence for efficacy for inositol, a natural glucose isomer and a precursor of the intracellular phosphoinositol cycle.(Benjamin ea, 1995) Inositol is taken as a powder in juice in large volumes.

¹⁶⁵⁸ Uhde and Singareddy (2002) argue that caffeine sensitivity is greater in panic disorder than in other anxiety disorders and normals.

¹⁶⁵⁹ At least one year according to the APA.(2002, p. 674)

¹⁶⁶⁰ The receptors habituate.

¹⁶⁶¹ Inhibitory serotonergic projections from raphe to locus ceruleus decrease noradrenaline output.

¹⁶⁶² Particularly used for refractory cases.

¹⁶⁶³ Inexpensive, effective, and may be useful in SSRI-non-responders.(Welch ea, 2008, p. 546)

SSRIs need to be used in low dosage to start with, e.g. sertraline 50 mgs/day although usual antidepressant doses (occasionally higher) are often needed for a therapeutic response. They also reduce agoraphobic avoidance. Treatment of panic with antidepressants may cause an initial worsening of symptoms (this may not happen with MAOIs), so the rule is to start with a very low dose¹⁶⁶⁴. Alternatively, low doses of an antidepressant can be added to a BZD and then the dose of antidepressant can be slowly increased; when symptoms have been controlled for some weeks the BZD can be tapered slowly and eventually discontinued. Interestingly, research conducted during the early 1980s found that propranolol pretreatment failed to prevent lactate-induced panic attacks.(Gorman ea, 1983) Response to SSRIs takes at least 4 weeks, and a full response can take up to 12 weeks. Some patients who fail to respond fully to a TCA or an SSRI may respond to a combination of the two.(Tiffon ea, 1994) SSRI therapy, with the possible exception of fluoxetine, should not be abruptly discontinued after prolonged use.

Pharmacotherapy should be continued for a year before consideration is given to possible very slow tapering, e.g. a decrease in dosage every 4-8 weeks¹⁶⁶⁵.

Things to consider before deciding to taper pharmacotherapy

Duration and severity of panic disorder before treatment?

How effective was the drug?

How long was the patient stable on medication?

Stressors operating currently or anticipated?

Motivation of patient to stop treatment?

Understanding of risks, e.g. relapse, abstinence syndrome, possible teratogenicity?

Involvement and understanding of important others in patient's life?

Published complications of panic disorder include peptic ulcer, hypertension, increased mortality from suicide¹⁶⁶⁶ and cardiovascular disease, and abuse of alcohol and other substances. There is no evidence that mitral valve prolapse¹⁶⁶⁷, which is over-represented in panic disorder patients, makes a difference to history, course or response to treatment. However, Coplan ea (1992), in a series of 22 cases, found that treatment for panic disorder improved mitral valve prolapse on the echocardiogram. The direction of causality remains unknown: does panic disorder cause mitral valve prolapse (anxiety places a strain on the heart) or *vice versa*? However, to complicate matters further, mitral valve prolapse may be more common in certain other psychiatric disorders (such as bipolar disorder, GAD, and anorexia nervosa) than in panic disorder and may be associated with similar symptomatology as in panic disorder.(Levenson & Dwight, 2000) Gonzalez ea (2002) emphasise the methodological issues that need to be resolved (use of cardiac disorder control groups and a better definition of mitral valve prolapse) before the relationship between mitral valve prolapse and psychiatric disorders can be clarified. Finally, Hayek ea, (2005) in a review article, pointed out that recent studies found no excess of psychiatric symptoms (including panic disorder) in unselected outpatients participating in the Framingham Heart Study.

A poor prognosis is associated with female sex, hypochondriasis, comorbid depression, alcohol abuse, personality disorder, interpersonal sensitivity, side-effects of medication, failure to improve with treatment, longer duration of illness (Shinoda ea, 1999) and more severe phobic avoidance (agoraphobia) at baseline. Frequency of panic attacks at baseline does not predict symptomatic outcome.(Nutt ea, 2002, p. 34) The condition usually lasts for years and varies in severity over time, with less than half of patients being panic free after up to 20 years of treatment. However, there may, on average, be some amelioration of severity of symptoms in episodes of panic disorder, GAD, and social phobia with the passage of time.(Ramsawh ea, 2009) According to the APA,(2002, p. 676) comorbidity with current or past Axes I (e.g. bipolar disorder,

¹⁶⁶⁴ However, one should not make the mistake of settling for too low a final dose.

¹⁶⁶⁵ An exception might be a patient who becomes pregnant and wants to suddenly stop the medication.

¹⁶⁶⁶ It has been difficult to determine the **contribution of panic disorder *per se* to risk of suicide**. This is because of the very high levels of comorbidity, e.g. other anxiety disorder, affective disorder (unipolar, bipolar), personality disorder (especially common are the 'anxious cluster'), alcohol, caffeine, cannabis, cocaine, nicotine, nasal decongestants and other substance use (primary or secondary).

¹⁶⁶⁷ **Mitral valve prolapse** (floppy mitral valve) is a common cause of mild mitral regurgitation. Aetiology is congenital or myxomatous degeneration. May occur in connective tissue disorders (e.g. Marfan's syndrome). There is dyspnoea, tiredness, palpitations, and oedema/ascites. Benign arrhythmias and atypical chest pain may occur. Embolic CVA and TIAs are uncommon.

unipolar depression) and/or II (e.g. avoidant personality disorder) disorders is the rule rather than the exception.

4-year follow up of panic disorder patients (Katschnig ea, 1995)

Full remission 31%

Episodic course 24%

Persistent course 45%

2-year retrospective study of panic episodes in Dutch general population (Batelaan ea, 2010)

In panic disorder, 64.5% had a remission (mean time to remission 5.7 months)

43.3% still had panic after 1 year

21.4% of those with panic disorder who had remitted had a recurrence

Prognosis of subthreshold panic disorder better than for full syndrome

Remission predictors were being female, lack of ongoing problems, subthreshold status, and low initial panic attack frequency

Ondine's curse (congenital central hypoventilation syndrome)

This condition involves a reduced sensitivity of the brainstem leading to inadequate breathing, particularly when asleep. It is said that panic disorder is its opposite, (Pine ea, 1994) with a hypersensitive or false 'suffocation alarm' system.

Hyperventilation

Lactic acid induces hyperventilation. The symptoms of hyperventilation are dyspnoea, air hunger/suffocation, cold extremities, finger and perioral paraesthesiae¹⁶⁶⁸, tremor, chest pain/palpitation, nausea, abdominal distension, dizziness/fainting, feelings of unreality, and, rarely, tetany. The patient breathes with either an irregular sighing pattern or with a rapid, shallow, regular pattern. Pathogenesis includes neuronal hyperexcitability and vasoconstriction. As can be demonstrated by studying transcutaneous CO₂, hyperventilation is an important mechanism in panic attacks. Blood gas analysis shows hypocapnoea during the acute phase, but chronic cases may have normal CO₂ levels. Unilateral somatosensory symptoms, often left-sided, may be induced and confuse the clinician.

Stage fright (performance or situational anxiety)

Some of the symptoms of anxiety are due to alkalosis secondary to hyperventilation. Actors, and exam candidates, sometimes take propranolol (10-40 mgs) an hour before a performance.¹⁶⁶⁹ Oxprenolol (Trasicor), a partial agonist, causes less bradycardia than does propranolol. Breathing exercises (to slow down the rate of breathing) and re-breathing from a paper bag¹⁶⁷⁰ (to re-introduce one's own carbon dioxide) are useful treatments. The patient who believes he is going to die because of, say, palpitations, can be shown how his symptoms arise (by breathing fast and deep) and how they can be arrested (paper bag). According to Schmidt ea, (2000) breathing retraining did not add to the effectiveness of a particular form of CBT for panic disorder (panic control treatment); indeed it might even interfere with the maintenance of treatment gains! However, this was not the experience of Öst, (2004)

Post-traumatic stress disorder (PTSD)¹⁶⁷¹

'The diagnosis of PTSD may be appropriate in some cases, but physicians should not provide it reflexively in the aftermath of trauma'. (Rosen ea, 2008)

PTSD (O'Shea, 2001; North ea, 2009) is a syndrome¹⁶⁷² starting from days to years¹⁶⁷³ (Van Dyke ea, 1985) after significant psychological stress or trauma¹⁶⁷⁴. Following this time lag, chronic symptoms

¹⁶⁶⁸ Hyperventilation is the commonest cause of distal (face, hands, feet) paraesthesiae, sometimes unilateral and then more often left-sided.

¹⁶⁶⁹ Note: expert advice should be sought; for example, asthma may be induced by beta-blockers.

¹⁶⁷⁰ This can be dangerous in the presence of hypoxia or myocardial ischaemia. (Callahan, 1989)

¹⁶⁷¹ 'Gross stress reaction' was included in the first edition of DSM but failed to re-appear in DSM-II. The inclusion of clinical significance criterion in DSM-IV reduces the conditional probability of the disorder given trauma exposure by about 30%. Cases meeting the criterion are more pervasively and persistently disturbed. (Breslau & Alvarado, 2007) As pointed out by Lloyd (2007, p. 74) partial PTSD syndromes are likely to be more common than the complete syndrome.

¹⁶⁷² A number of authors suggest that PTSD is a superfluous label and could be covered by other disorders of anxiety/mood, or that it was included in DSM-III because of post-Vietnam political pressure. (Kelsey ea, 2006, p. 167) It should be noted that terrorism has effects on the general population, e.g. persistent if diminishing stress, perceived stress to self, reduction in travel, and a more negative world view 7 months after the July 2005 London bombings. (Rubin ea, 2007)

develop that can cause severe social and occupational incapacity.¹⁶⁷⁵ The *DSM-IV criteria* include exposure to a traumatic event with serious injury or threat of injury to self or others associated with intense negative affect. As more combat veterans survive physical trauma doctors will need to prepare for increased rates of psychiatric problems, particularly PTSD, and combat veterans tend to respond less well to interventions than do civilians with PTSD. (Richardson ea, 2010) PTSD causes a major drain on numbers available for combat. (Cohen ea, 2010) Children may exhibit disorganized or agitated behaviour. The traumatic event is persistently re-experienced with distressing recollections.

Children

- Young children may act out the traumatic event in repetitive play
- Child disaster survivor's prognosis may depend largely on the mother's response to the event (Nolen-Hoeksema & Morrow, 1991)
- Chiefly teenage school children on tour ship *Jupiter* in Mediterranean which sank – 52% of survivors developed PTSD; 30% were recovered by 1 year and 34% continued to have PTSD at follow-up (Yule ea, 2000)
- Combat injury in military service members affects both child (especially if there was family distress/disruption before injury; spouse-reported injury severity was not related to child distress) and family functioning (Cozza ea, 2010)

Childhood risk factors for later PTSD

Depression-anxiety and behavioural problems may increase risk for PTSD by increasing vulnerability to PTSD effects of trauma exposure and indirectly by increasing chances of exposure to assault. (Storr ea, 2007)

Koenen ea (2007) followed children born in New Zealand born 1972-3: assessed at ages 26 and 32; at age 26, increased risk of trauma exposure and PTSD was associated with childhood externalizing characteristics and family environmental stressors (maternal distress and loss of a parent); there was an increased risk of PTSD only with low IQ¹⁶⁷⁶ and chronic environmental adversity; low IQ at age 5 years, antisocial behaviour, and poverty before age 11 predicted PTSD due to traumatic events occurring between ages 26-32.

Recurrent, distressing dreams of the traumatic event¹⁶⁷⁷ are experienced. The patient acts or feels as if the traumatic event is recurring, including experiencing illusions or hallucinations.

The core problem in PTSD may be a failure to integrate the traumatic experience leading to memories of the trauma dominating consciousness. Breuer¹⁶⁷⁸, Freud's mentor, noted the release of intense affect by hypnotised patients and interpreted this as representing feelings that underlay presenting symptomatology

¹⁶⁷³ **Delayed onset of PTSD** is controversial and was introduced by DSM III following observation of soldiers not developing symptoms until they returned home. Andrews ea (2007) performed a systematic study and found that de novo delayed-onset cases were rare, but that delayed onset representing reactivation of earlier symptoms accounted for 38.2% and 15.3% of military and civilian PTSD respectively. Hepp ea (2008) followed cases of severe injury for three years: PTSD was present in 6%, 2%, and 4% at 2 weeks, 1 year and 3 years post-injury; persisting PTSD at 6 months or delayed onset were associated with chronicity. Heir ea (2009) examined Norwegians exposed to the 2004 tsunami and found that recalled threat increased from 6 to 24 months and that recall amplification was associated with lack of improvement in PTSD symptoms. Frueh ea (2009) found that delayed onset of PTSD is very rare among US war veterans one year after trauma and they found no cases starting 6 or more years after the event.

¹⁶⁷⁴ Lt. Audie Murphy (1924-71) suffered from PTSD. Combat has probably always produced PTSD or its equivalent. See, e.g. McPherson (1990, p. 734) on the American Civil War. During WWI the French used 'forward psychiatry' or 'PIE' (proximity to battle, immediate treatment and expectancy of recovery, including return to duty) to reduce troop losses but, according to Jones ea, (2007) it was ineffective. Delayed onset might be triggered by a recent reminder of past trauma – Kelsey ea (2006, p. 169) give the example of a mother who suffered childhood abuse who develops PTSD when her offspring near the age at which she was abused.

¹⁶⁷⁵ In DSM-IV the symptoms may appear in excess of 6 months after the event and last for longer than one month; ICD-10 has no duration specifier and states that the onset of symptoms rarely exceeds 6 months. One problem with studying PTSD is the inconsistency with which people report potentially traumatic events. (Hepp ea, 2006) Scott and Stradling (1994) argue that PTSD may follow a single trauma of the type mentioned in DSM but that it may also follow prolonged duress.

¹⁶⁷⁶ Lower IQ may be a predisposing factor in adults for PTSD. (Kremen ea, 2007)

¹⁶⁷⁷ Frightening dreams of obscure content in minors.

¹⁶⁷⁸ Josef Breuer (1842-1925), Austrian physician, is known for his work with Anna O and the Hering-Breuer reflex.

but had dated back to earlier trauma which had not found emotional expression. William Halse Rivers (1864-1922), medical officer at Craiglockhart War Hospital, realised this when treating WWI cases of 'war neurosis'. (Rivers, 1923) He believed that the worst symptoms could be explained better by the patient's attempts to repress memories rather than the trauma itself. In order to integrate an experience we must develop a coherent internal representation of it. Janet¹⁶⁷⁹ (1923) wrote that the traumatised individual could not form a memory of the 'unassimilated happening'. A similar hypothesis was developed by Browne¹⁶⁸⁰ (1990; Magee ea, 1984): 'the unexperienced experience'¹⁶⁸¹.

The sufferer is deeply distressed and physiologically aroused when exposed to internal or external reminders of traumatic event. Persistent avoidance of internal and external stimuli associated with the traumatic event occurs. There is numbing of general responsiveness and persistently increased arousal, e.g. insomnia, irritable or explosive, poor concentration, excessive vigilance, and exaggerated startle response. The syndrome lasts more than 1 month and interferes significantly with functioning. It can be 'acute'/short duration (< 3 months) or chronic (3 months or more). Finally, one can specify if PTSD onset is delayed by at least 6 months after the traumatic event. Some cases may not become fully apparent for much longer. The point prevalence of PTSD in the general population is about 1%. It is chronic or recurring in a high proportion of cases: 12 (29%) of survivors of the 1966 coal slag heap collapse into a school in Aberfan (Wales) met diagnostic criteria for current PTSD at 33-year follow-up.(Morgan ea, 2003) In their systematic review, Fazel ea (2005) calculated that 9% and 5% of refugees resettled in western countries had PTSD and major depression respectively, with 11% of children in this category having PTSD. Studies of MZ and DZ twins who had served with US forces in Vietnam suggest a genetic component in PTSD. Indeed, twin studies suggest that exposure to trauma, perhaps as a function of personality, and subsequent PTSD may be genetic.(Stein ea, 2002) Transgenerational PTSD has been described. Personality disorders of all types are common among patients with PTSD, and there may be no specific relation with borderline personality disorder.(Golier ea, 2003) Intensity of exposure, perceived threat, and losses sustained in the disaster, were not predictive of PTSD in Australian bushfire fighters in early reports but later work (Parslow ea, 2006) suggested that feeling very distressed or being evacuated were strongly associated with PTSD in young adults; introversion, neuroticism, and a past personal or family history of psychiatric disorder were premorbid factors significantly associated with the development of chronic PTSD. A prospective cohort study of US military personnel found that poor mental or physical health before combat exposure significantly increased the risk of symptoms or diagnosis of PTSD following deployment.(LeardMann ea, 2009) Kleim ea (2007) looked at assault survivors and found that mental defeat, rumination, and previous anxiety or depression predicted chronicity. British body-handlers in the Gulf were prone to develop PTSD if they had a past history of psychological problems or if they believed their lives were endangered. British reservists¹⁶⁸² who took part in the 2003 Iraq War were more likely to reported higher exposure to traumatic experiences than were their regular colleagues, yet PTSD related more to domestic problems than events in Iraq!(Browne ea, 2007) Intense stressors were specifically linked to PTSD in a study of Vietnam veterans. The presence of symptoms after 5 years in veterans of the Falklands War was associated with the intensity of combat experience as well as retrospective reporting of emotional problems in the initial period on return home from the war. Interpretation of combat-related PTSD data should be tempered by the knowledge that soldiers may exaggerate or misrepresent their combat involvement.(Frueh ea, 2005) However, heavy combat and low rank was associated with PTSD, anxiety and depression in Australian veterans 50 years after the Korean War.(Ikin ea, 2007) Personal appraisal of threat to life during trauma was the most important predictor of PTSD symptoms in a study of UK soldiers.(Iversen ea, 2008) Proximity to an earthquake epicentre and to a fatal playground shooting by a sniper predicted severity of PTSD in Armenian and Los Angeles children respectively (Nolen-Hoeksema &

¹⁶⁷⁹ Pierre Marie Félix Janet (1859-1947), famous for his discovery of dissociation.

¹⁶⁸⁰ Ivor Browne (b. 1929), Irish psychiatrist.

¹⁶⁸¹ According to Browne (2008) when a person experiences an overwhelming experience they 'freeze' (as happens to an animal caught by a predator: O'Shea, 1988) and fail to 'integrate' the experience into memory so it remains unsettlingly in the present as if it was happening now. If a later stressor activates the non-integrated material an emotionally painful flashback occurs which is imperfectly repressed.

¹⁶⁸² Reservists were older and of higher rank than regulars. They tend to be demobilised quickly, thus denying time for processing adversity.

Morrow, 1991) and actual combat exposure is associated with greater self-reporting of PTSD in US troops than is being deployed but not exposed. (Smith ea, 2008) However, Booth-Kewley ea (2010) used a questionnaire and the PTSD Checklist (cut-off score of 44, 17.1% screened positive for possible PTSD) with over one-and-a-half-thousand US Marines deployed in Iraq and Afghanistan during 2002-7: deployment-related stressors, combat exposure, marital status, and education were significant associations with possible PTSD, but deployment-related stressors had the strongest association. Greater intensity of fear during an earthquake has been reported as strong risk factor for PTSD. (Basoglu, 2004) Elderly Israeli Holocaust survivors were excessively sensitive to the events of the Gulf War. Interestingly, Sharon ea (2009) found that Holocaust survivors, 6 decades after the event, had increased lifetime and 12-month anxiety disorders, more current sleep problems and emotional distress, but no excess of depression or PTSD compared to controls.

Survivors of a mass shooting in Texas had high levels of pre-existing PTSD, although this did not predict post-disaster PTSD. Also, a history of other pre-disaster psychiatric disorders did predict post-disaster PTSD in females only. Nevertheless, most subjects who developed PTSD had no history of psychiatric illness. Research on people working at the World Trade Center site in New York (September 11, 2001: '9/11') by Perrin ea (2007) found that workers with less prior disaster training or experience were more likely to develop PTSD.¹⁶⁸³ Significant psychiatric symptoms (see box) were found in 'Ground Zero'¹⁶⁸⁴ ('9/11') ironworkers (Katz ea, 2009); risk factors included alcohol misuse, injury to or death of a family member/friend/co-worker at Ground Zero, and at least one adverse life event subsequent to September 11, 2001. Although subject to methodological problems, the research of Claassen ea (2010) suggest that the suicide rates fell in areas surrounding the World Trade Center after 9/11.

Psychiatric symptoms among ironworkers at Ground Zero 14-17 months post 9/11 (Katz ea, 2009)

	Ironworkers%	General population% ¹⁶⁸⁵
PTSD	18.5	3.5
Panic attacks	3.2	2.7 ¹⁶⁸⁶
GAD	6.5	3.1
Depression	5.7	6.7 ¹⁶⁸⁷
Positive CAGE	39.3	3.1 and 1.3 ¹⁶⁸⁸

PTSD, posttraumatic stress disorder; GAD, generalised anxiety disorder; CAGE, measure of problematic alcohol intake. Note: 67.7% of participants drank alcohol. 44% increased alcohol intake after 9/11, 36.8% at Ground Zero, and 63.8% after leaving the site. Of the 67.7% who drank alcohol 39.3% were CAGE-positive. 124 (including 1 female) ironworkers participated and 58.9% of these screened positive for psychiatric symptoms.

The prevalence of clinically significant PTSD, depression and anxiety in Sri Lanka 20-21 months after the 2004 tsunami was 21%, 16% and 30% respectively (Hollifield ea, 2008); believing ones life was in danger was the exposure item most strongly associated with symptoms and impairment; and personal strength, family and friends, a Western-style hospital, and religious practice helped in coping.

Exposure to trauma is not random in the general population. (Breslau, 2002) Childhood physical or sexual abuse and lack of religious faith may be predisposing factors for PTSD.

Lack of social support among tortured political Turkish ex-prisoners predicted anxiety and depression, but not PTSD. Negative responses from close others may be more predictive of PTSD in women than in men. (Andrews ea, 2003) Social stigma after surviving a major adverse event, such as the Chernobyl or Nagasaki explosions, although not thoroughly researched, probably acts as a risk factor for PTSD. (Nolen-Hoeksema & Morrow, 1991) Direct experience of violence and poverty increased the risk of PTSD in post-

¹⁶⁸³ Overall PTSD prevalence among rescue/recovery workers = 12.4%; police = 6.2%; unaffiliated workers = 21.2%.

¹⁶⁸⁴ This means the actual site (World Trade Center) where 2 jetliners crashed into the towers in 2001.

¹⁶⁸⁵ 12-month prevalence rates.

¹⁶⁸⁶ Panic disorder.

¹⁶⁸⁷ Major depression.

¹⁶⁸⁸ For alcohol misuse and dependence respectively.

conflict Northern Ireland whereas strong national identification appeared to be protective.(Muldoon & Downes, 2007)

Disasters offer the researcher a chance to avoid some of the methodological problems inherent in life event research because of the wide range of people affected.(Bromet & Havenaar, 2002) Having studied a population before disaster strikes is an added bonus. For example, pre-disaster symptomatology was the strongest predictor of post-disaster symptom severity in one study of Californian university students before and after an earthquake.(Nolen-Hoeksema & Morrow, 1991)

PTSD may be particularly common in soldiers who have suffered acute combat reactions.(Solomon & Mikulincer, 2006) Tokyo firefighters who developed signs of Sarin nerve gas poisoning were more likely to develop PTSD than people who showed only mild, or no, intoxication.(Bromet & Havenaar, 2002) Civilians may develop PTSD after a natural catastrophe, a criminal assault, burglary, divorce, loss of career, concentration camp experiences, rape (Osterman ea, 2003), industrial or traffic accidents¹⁶⁸⁹ (Hepp ea, 2008), air crashes, and terrorist/ hostage experiences.(Galea ea, 2002; Mol ea, 2005) The relatives of murder victims may suffer PTSD and other adverse sequelae.(Mezey ea, 2002) PTSD may occur in as many as 94% of rape victims immediately following the event, this figure halving after 3 months. In the USA, the event most likely to be associated with PTSD is rape for both sexes, followed by threat with a weapon for women and combat for men, with a median duration of the syndrome of 64 months in those not receiving treatment. A prisoner who experiences the hanging of a cellmate may develop PTSD. Chronic PTSD may have adverse effects on offspring. Doctors who had been sued and people who have rescued others may develop PTSD. PTSD has followed traumatic childbirth¹⁶⁹⁰. 17% of train drivers who experienced suicides developed PTSD, and even more developed other psychiatric problems.(Farmer ea, 1992)

Dissociative symptoms experienced at the time of an injury, considered as a strategic response to limit arousal¹⁶⁹¹, may be predictive of later PTSD,(e.g. Birmes ea, 2003) whereas loss of consciousness after a noxious event has been reported by some, but not all, researchers as being protective against developing the syndrome. Persistent dissociation rumination four weeks after a road traffic accident was reported by Murray ea (2002) to be associated with the development of chronic PTSD.

PTSD has a strong positive association with the experience of torture, especially if the torture is perceived as being severe and if the effects on the family of the victim are catastrophic.

The symptoms may be divided into core symptoms and depression/anxiety. Core symptoms are due to re-experiencing the original traumatic event. There is numbing of responsiveness to, or reduced involvement in, the external world, and a variety of autonomic, dysphoric, or cognitive symptoms.

Rape and other forms of sexual violence

Increasing worldwide

At least 20% of women experience rape or attempted rape during life (Welch J & Mason, 2007)

Some authorities put the lifetime risk for rape at up to 50% for women (Bowyer & Dalton, 1997)

About 5% of rape victims become pregnant as a result of the assault and 4% to 56% develop a sexually transmitted infection (Wilken & Welch, 2003)

Rape victims initially may experience shock, disbelief, guilt and shame; days to weeks later they may appear to improve, but then become depressed for many months

Prolonged reactions are associated with:

- Prior psychological or physical problems
- Low socio-economic status

¹⁶⁸⁹ Intrusive symptoms shortly after an accident predicted PTSD.(Hepp ea, 2008)

¹⁶⁹⁰ Olde ea (2005) reported a 2.1% incidence of PTSD among 140 women after childbirth. Perinatal negative emotional or dissociative reactions predicted PTSD at 3 months postpartum. Mangaoang (2009) points out that changes in DSM-IV from previous editions have 'allowed' the inclusion of events within normal experience (e.g. childbirth) within diagnostic decision-making for PTSD.

¹⁶⁹¹ An fMRI study (Felmingham ea, 2008) of dissociated PTSD subjects found increased activation of ventral prefrontal cortex (PFC) in response to conscious fear (shown a fearful face) and of bilateral amygdala, insula and left thalamus in response to non-conscious fear (employing backward masking) when compared to people with non-dissociated PTSD; comparatively, dissociated PTSD subjects had reduced activation in dorsomedial prefrontal regions for conscious fear faces. The authors interpret the results as suggesting that the 'strategic response to limit extreme arousal' role of dissociation operates only when the person consciously processes threat, i.e. enhanced PFC and limbic activity accompanies conscious and non-conscious fear respectively in dissociated PTSD.

- Repeated assaults
 - Alcohol or other substance abuse
- Management principles:
- Cognisance of victim's desires and requirements
 - Time since assault
 - Police involvement
 - Meticulous note-keeping
 - Safety¹⁶⁹²
 - Attention to traumatic sequelae
 - Forensic examination (including samples for DNA)
 - Emergency contraception, etc

*Survivor guilt*¹⁶⁹³ is said to be common among Holocaust survivors and their offspring. Guilt about conduct during combat appeared to strongly predict suicide attempts and preoccupation with suicide in Vietnam veterans with PTSD.¹⁶⁹⁴

War veterans have very high current and lifetime diagnosable major depression.

Low 24-hour urinary cortisol excretion (Young & Breslau[2004] found normal mean urinary cortisol levels) and increased levels of lymphocyte glucocorticoid receptor numbers have been reported in PTSD, which may reflect increased negative feedback sensitivity at one or more levels of the hypothalamic-pituitary-adrenal axis. Young & Breslau (2004) found that trauma as such does not lead to sustained increases in cortisol or catecholamine levels but that PTSD is associated with raised catecholamine levels, and women with PTSD and comorbid major depressive disorder had higher cortisol levels than women with neither disorder or with either disorder alone.

The DST is hyper-negative in PTSD, with enhanced suppression of cortisol. Changes in DNA methylation, or some other mechanism, may underlie some cases of transgenerational PTSD.(Yehuda ea, 2007) In one study (Yehuda ea, 2004) ACTH and cortisol responses to 0.5 mg of dexamethasone were assessed in people with PTSD and in normal controls; PTSD subjects had greater suppression of cortisol and ACTH; the authors interpret their findings to mean that there is enhanced cortisol negative feedback at pituitary level.

Meewisse ea (2007), in a systematic review and meta-analysis, found that overall PTSD patients and controls do not differ in cortisol levels. Low cortisol in patients were more likely if controls were not exposed to trauma, if the patients were female, if there was a history of physical or sexual abuse, or if the samples were taken in the afternoon. The authors admitted that publication bias might have affected their findings.

Adrenergic hyperactivity may be important in the development of PTSD because of certain findings in sufferers:

- (a) increased physiological responsiveness, such as raised blood pressure, to stressful stimuli, or a tachycardia shortly after the traumatic event
- (b) long-standing increases in the urinary catecholamines adrenaline and nor-adrenaline
- (c) lactate and yohimbine, which stimulate the arousal system, cause flashbacks
- (d) positive symptoms (like intrusive memories and hyperarousal) were improved in an open study by adrenergic blocking drugs such as clonidine and propranolol.

An increased level of T3 occurs in PTSD.(Mason ea, 1994)

Pain following injury increases the risk for PTSD (Norman ea, 2008) and adequate analgesia after combat analgesia may reduce the risk for later PTSD.(Holbrook ea, 2010)

Males with a past history of PTSD have been demonstrated to have suppression of cellular immunity.

¹⁶⁹² E.g. in the case of domestic assault a refuge may be required.

¹⁶⁹³ Person feels that he does not have the right to live when so many others were killed.

¹⁶⁹⁴ People from some nations, such as British soldiers from the Falklands War, appear to have functioned better socially than did Vietnam veterans who more often failed to take up ordinary roles, were violent, or practised self-destructive behaviour. This difference may have been due to the different receptions received on returning home.

Hippocampal volume has been reported as diminished in PTSD and might be due to PTSD itself or may relate to the high comorbidity, including alcohol abuse, associated with this syndrome or it might be due to stress.(Winter & Irlle, 2004) Some MRI research suggests that reduced hippocampal volume in PTSD may only apply to chronic or complicated cases,(Bonne ea, 2001; Vythilingam ea, 2002) although this is not entirely certain.(Lindauer ea, 2005) Combat-exposed veterans were reported to have smaller cortical volumes (MRI) especially in the region of parahippocampal gyrus, superior temporal cortex, lateral orbital frontal cortex, and pars orbitalis of inferior frontal gyrus.(Woodward ea, 2009) 17 male veterans with combat trauma and PTSD had reduced volumes of CA3/dentate gyrus subfields on MRI.(Wang ea, 2010) To complicate interpretation, a twin study (Gilbertson ea, 2002) suggested that smaller hippocampal volume may be a risk factor for PTSD rather than a consequence of trauma. Bremner ea (2003) conducted MRI and PET on three groups of women: a history of childhood sexual abuse (CSA) plus PTSD was associated with failure of hippocampal activation and reduced (by 16%) hippocampal volume compared to women with CSA but no PTSD, and women with CSA and PTSD had a 19% smaller hippocampal volume relative to women without either problem. Effective psychotherapy is not associated with return of hippocampal volumes to normal.(Lindauer ea, 2005) There is evidence for increased activation of the amygdala after symptom provocation with simultaneous reduction in activity of Broca's area. The latter findings may relate to the role of the amygdala in emotional memory and, in the case of Broca's area, a problem in labelling experience.(Hull, 2002) Shin ea (2004) employed PET a script-driven imagery paradigm in Vietnam veterans with and without PTSD: veterans with PTSD exhibited reduced rCBF in medial frontal gyrus during traumatic (v neutral) script-driven imagery; such changes were inversely correlated with rCBF changes in the left amygdala and the right amygdala/periamygdaloid cortex; in the traumatic condition, symptom severity related positively to rCBF in the right amygdala and negatively to rCBF in the medial frontal gyrus. The authors interpreted their findings as supporting a reciprocal relationship between the medial prefrontal cortex and the amygdala in PTSD. Using a cross-sectional design including MZ twins discordant for trauma exposure, Shin ea (2009), using PET and fluorodeoxyglucose 18, found that veterans with PTSD and their co-twins had significantly higher resting regional cerebral metabolic rate for glucose in dorsal anterior cingulate cortex/mid-cingulate cortex compared to veterans without PTSD and their co-twins; resting regional cerebral metabolic rate for glucose in the same areas in unexposed co-twins correlated positively with combat exposure, severity of PTSD, and use of alcohol in their exposed twins; the authors suggest that resting metabolic activity in dorsal anterior cingulate cortex/mid-cingulate cortex may represent a familial risk factor for PTSD should exposure to psychic trauma follow.

Meta-analysis of functional neuroimaging (fMRI and PET) of emotional processing in anxiety (Etkin & Wager, 2007)

Subjects: PTSD, social anxiety disorder, specific phobia, and fear conditioning in healthy people

All 3 disorders: greater activity than healthy people in amygdala and insula¹⁶⁹⁵

Increased activity in amygdala and insula seen more often in social anxiety disorder and specific phobia than in PTSD

Only PTSD associated with decreased activation in dorsal and rostral ventromedial prefrontal cortex¹⁶⁹⁶

Peres ea (2007) employed SPECT and a script-driven symptom provocation paradigm with subthreshold PTSD cases and found increased activity in parietal lobes, left hippocampus, thalamus and left prefrontal cortex during memory recall after psychotherapy.

According to Neumeister ea,(2003, p. 761) there may be impairment of the neural processes mediating extinction of trauma-related stimuli in PTSD patients. Electrophysiological response to an increase in intensity of a tone may be different in (combat-related) PTSD¹⁶⁹⁷ to normal¹⁶⁹⁸,(Lewine ea, 2002) although not all cases have this response. Early-onset PTSD has been shown in a small study to be associated with

¹⁶⁹⁵ Structures linked to negative emotional responses.

¹⁶⁹⁶ Structures linked to experience/regulation of emotion.

¹⁶⁹⁷ No increase in P200 magnitude with increase in tone intensity.

¹⁶⁹⁸ Linear increase in P200 magnitude with increase in tone intensity.

an abbreviated REM period before sleep stage change or awakening and increased number of REM episodes during sleep¹⁶⁹⁹.(Mellman ea, 2002)

Bryant (2008) discussed the relationship between mild traumatic brain injury (MTBI) and PTSD.(see Hoge ea, 2008) Exaggerated amygdala¹⁷⁰⁰ response impairs regulation (inhibition) of the amygdala by the medial prefrontal cortex (MPC); during fear processing in PTSD there is decreased activation of the MPC and the latter may be damaged by shearing forces (against bone) in MTBI; also, MTBI may impair cognitive capacity to manage traumatic memories and diminish the ability to engage cognitive strategies to manage disturbing experience¹⁷⁰¹. In a study by Carlson ea (2010) of US veterans screened for traumatic brain injury (TBI) by Department of Veterans Affairs facilities over 80% of those with positive TBI screens had psychiatric diagnoses; positive screen but unconfirmed TBI status were at increased risk for having PTSD as well as having depression or substance-related diagnoses; and clinically confirmed TBI status was associated with increased likelihood of having PTSD, anxiety, and adjustment disorders. Excess intake of alcohol (Thomas ea, 2010) and an increased risk of dementia (Yaffe ea, 2010) have been reported in veterans with PTSD.

An Australian study (Dileo ea, 2008) found that male war veterans with PTSD had significant olfactory identification deficits compared to controls. The authors suggested that this suggested a role for orbitofrontal dysfunction in PTSD.

Although not set in stone, as for affective and social phobia, the short (S) allele of the 5-HTT gene may be implicated in PTSD (Lee ea, 2005), as may the long L_A allele.(Grabe ea, 2009) Xie ea (2009) found that the 5-HT transporter 5-HTTLPR genotype (5-HTT promoter length polymorphism) did not predict onset of PTSD on its own but that it interacted with adult traumatic events and childhood adversity (both of which themselves predicted PTSD) to increase risk for PTSD, especially for people with high rates of adult traumatic events and childhood adversity.

Changes in acetylcholinesterase metabolism may persist for long periods after a single stressful event. In mice exposed to stress there is a change in the production of the commonly prevalent synaptic membrane-bound form of the enzyme to a normally rare soluble form, which may compromise capacity to cope with intensified cholinergic stimuli. Stressed *in vitro* mouse hippocampal neurones demonstrate very strong responses to electrical stimulation in the presence of physostigmine. Also, the muscarinic antagonist atropine blocks the response in post-stress neurones more effectively than in controls. There is also evidence for involvement of glutamine in these oversensitive synapses.

Pre-clinical research suggests that neuropeptide Y (NPY) may be anxiolytic and PTSD subjects may have low baseline NPY levels and a blunted NPY response to yohimbine.(Nijenhuis ea, 2002) However, research findings have been conflictual (Seedat ea, 2003) and it may be that reduced NPY levels are due to trauma exposure as such rather to PTSD.

The Mississippi Scale for Combat-Related Post-Traumatic Stress Disorder

Self-report inventory measuring symptom severity and effects on coping

Combat Exposure Scale

Subjective measure of wartime stressors, light stress scoring 1, heavy combat exposure scoring 5

The Structured Interview for Posttraumatic Stress Disorder

Questions asked of patient; delivers a score; event is defined, e.g. captivity, complicated bereavement, witness to death from murder or injury, combat, assault, experiencing threats or a close call, and being injured

MMPI

May predict vulnerability to PTSD symptoms in men prior to combat

Differential diagnosis: Only a minority of those exposed to trauma develop PTSD,(Stein, 2003, p. 41) and there are other outcomes following trauma exposure, including major depression¹⁷⁰².(Marshall &

¹⁶⁹⁹ Such REM fragmentation is not a surprising finding.

¹⁷⁰⁰ The amygdala is important to developing and expressing conditioned fear reactions.

¹⁷⁰¹ E.g. an inability to view traumatic experience as non-permanent.

¹⁷⁰² The chief symptoms among both survivors and relatives in the Herald of Free Enterprise disaster were sleep problems, loss of concentration and anger. The main diagnoses were PTSD, other anxiety states, and depression. Bereavement was associated with grief and depression, whereas non-bereaved passengers were anxious. Women tended to have affective symptoms and men showed an

Rothbaum, 2004; Toomey et al., 2007) Fear et al. (2010) examined the consequences of deployment to Iraq and Afghanistan on the mental health of the UK armed forces and found a low prevalence (4%, especially among reservists) of probable PTSD. The most frequently reported symptoms in this cohort were those related to common mental disorders (19.7%) and misuse of alcohol (13%, especially among regular soldiers). Spouses of soldiers deployed to foreign combat zones are at increased risk of depression, sleep problems, anxiety, acute stress reactions and adjustment disorders. (Mansfield et al., 2010)

Subsyndromal PTSD: Where do patients fall in the classificatory system if they fail to fulfil strict diagnostic criteria for PTSD? For example, van Zelst et al. (2003) found a six-month prevalence of PTSD in 0.9% of elders but 13.6% had symptoms short of full PTSD.¹⁷⁰³ Also, subsyndromal PTSD has escalated to full PTSD during the fiftieth anniversary of the Second World War! (Hilton, 1997) This change appears to have been provoked by media coverage (re-traumatisation).

Acute stress reaction (ASR): This is defined by ICD-10 as a reaction to severe stress that lasts from hours to 3 days. According to DSM-IV-TR, acute stress disorder (ASD) lasts from 2 days to 4 weeks and occurs within 4 weeks of the traumatic event¹⁷⁰⁴. The core symptoms are anxiety (threat) or depression (loss), experienced singly or together. DSM-IV-TR stresses dissociative symptoms¹⁷⁰⁵. It may persist as an adjustment disorder or PTSD, although many people not meeting ASR/ASD criteria still develop PTSD. (Marshall & Rothbaum, 2004, p. 123; Dalgleish et al., 2008) 'Battle exhaustion' or 'battle shock' is an acute, disabling reaction to war that can be seen as 'normal'; most cases recover. Cases should be seen early, mutual support groups are important, and emphasis in therapy should be on the here and now. Very severe cases may experience intense fear, hyperarousal, and 'hysterical' symptoms¹⁷⁰⁶. Others may be withdrawn, apathetic or mute. Support, rest and reassurance are essential, any deeper evaluative approach being deferred. There is evidence that exposure-based treatment may be associated with less intensive PTSD symptoms subsequently than when treatment is with cognitive restructuring. (Bryant et al., 2008b)

Adjustment reaction/disorder (AD): This psychological reaction to new circumstances is divided in ICD-10 into depressive, mixed anxiety-depressive, other emotional, and conduct (with or without emotional) subtypes and in DSM-IV-TR into anxiety, mixed anxiety-depressive, conduct disturbance, mixed emotion-conduct, and unspecified¹⁷⁰⁷ subtypes. AD can last for months to years. DSM-IV-TR criteria state that AD occurs within 3 months of 'identifiable stressor(s)' and it divides AD into 'acute' (duration < 6 months) and 'chronic' (6 months or longer). Before DSM-IV, a duration greater than 6 months necessitated a change in diagnosis. Subtyping of the chronic form is almost the same as in ICD-10. Previous experience and personality, as well as the precipitating event may help in understanding the reaction and intellectual disability is an important predisposing factor. In practice, attributing weight and an aetiological link to the stressor is often easier said than done. (Strain & Newcorn, 2003, p. 770) AD may differ from PTSD in that the stressors are usually less severe (Turner et al., 2005) and within the range of common experience; also, the classical symptoms of PTSD, such as re-experiencing the trauma, are absent. At least in theory, AD should be distinguishable from 'mixed anxiety-depressive' disorder by the lesser weight given in the latter state to a precipitating stressor. In reality, it is often not easy to distinguish AD from other psychiatric diagnoses and, in the milder case, normal reactions to adversity. AD may co-exist with another Axis I diagnosis. AD is often viewed as a diagnosis falling below the threshold for other conditions but this is no comfort for those saddled with the symptoms. Management of AD is similar to that for ASR. The patient should be helped to face his problems and not to avoid situations. Whilst psychotherapy (environmental manipulation, learning to cope with persistent stressors, and developing a support system) is considered to be the primary treatment approach SSRIs may be a safe option when an antidepressant is indicated. Prognosis may be

excess of substance abuse. Reluctance to discuss symptoms and a refusal to attend a psychiatric clinic were common. Generalised anxiety disorder and phobic anxiety disorder have been reported to be more common than PTSD after road traffic accidents. There are a number of reports of falsified PTSD from the military. The main conditions to consider are as follows.

¹⁷⁰³ Interestingly, van Zelst et al. (2003) found that neuroticism and adverse childhood events were risk factors.

¹⁷⁰⁴ Basically, it is either short-lived/subthreshold PTSD (Widiger & Mullins-Sweatt, 2007, p. 13) or 'acute' PTSD (Gilbertson et al., 2008, p. 468).

¹⁷⁰⁵ These **dissociative symptoms** can occur during or shortly following exposure to the traumatic event and consist of subjective numbing/detachment/emotional responsiveness, decreased awareness of surroundings (feeling dazed), derealisation/depersonalisation, and inability to recall some important part of the trauma (dissociative amnesia).

¹⁷⁰⁶ Whilst Kelsey et al. (2006, p. 171) suggest that dissociative symptoms are the chief symptoms of acute stress disorder Gilbertson et al. (2008, p. 467) point out that the emphasis on this phenomenon has been questioned.

¹⁷⁰⁷ A patient who refuses to consciously acknowledge (denial) medically-diagnosed lung cancer and who does not adhere with the treatment plan could be seen as having an 'unspecified' adjustment disorder.

better for adults than for adolescents, AD more often being a forerunner of other psychiatric problems in the latter. (Andreasen & Hoenk, 1982) Should AD evolve into another psychiatric disorder then the latter will need appropriate attention.

Brief psychotic disorder (DSM-IV): Classically, reactive psychosis results from massive stressors related in time to the disorder, it follows a benign course, and the content of the psychosis often reflects the nature of the traumatic experience. A good prognosis is associated with good premorbid functioning, few premorbid schizoid traits, severe precipitating stress, acute onset, affective symptoms, confusion and perplexity, little blunting of affect, short duration, and no family history for schizophrenia.

Enduring personality change after catastrophic experience (ICD-10): This applies to late chronic sequelae of devastating stress. It lasts at least 2 years, and manifests decades after a devastating stressful experience that would affect anyone adversely, e.g. torture, concentration camp experiences, or hostage situations. PTSD may precede it. The clinical features include hostility, mistrust, social withdrawal, feelings of emptiness and hopelessness, feeling threatened and estranged. Organic aetiologies, such as brain damage, are incompatible with the diagnosis.

Other specific phobias include panic disorder with agoraphobia (fear of having a panic attack) and social phobia (fear of being judged by others and/or embarrassing oneself in public¹⁷⁰⁸). Schizophrenic or other psychoses (delusion-based avoidance) and obsessive-compulsive disorder (avoidance of, e.g., dirt or contamination) are not examples of true phobias. Avoidance is based on the initiating trauma in PTSD.

Management: It is important to treat pain adequately following injury. (Norman ea, 2008) Exposure to memories of the traumatic stimulus constitutes a therapeutic factor common to all major theoretical models. Good managerial and organisational factors may have avoided PTSD among police officers that had been involved in retrieval and identification of human remains after a major disaster. However, psychological debriefing and brief counselling of British soldiers who handled dead bodies during the Gulf War did not affect subsequent psychiatric morbidity. Ismail ea (2002) found that Gulf War veterans had no more PTSD than did other veterans; this conclusion is supported by a systematic review. (Stimpson ea, 2003) A controlled (groups based in Bosnia, Gulf, and elsewhere) follow-up of Gulf War veterans (Hotopf ea, 2003) showed a moderate reduction in fatigue and psychological distress but a slight worsening of physical functioning, findings that were interpreted by Clauw (2003) as supporting the contention that these symptoms were not due to a specific environmental exposure (i.e. they are due to a variety of stresses, incl. war) and that they constituted a chronic syndrome similar to chronic fatigue (supported by Ismail ea, 2008), irritable bowel syndrome, or fibromyalgia, what Colonel Deahl, (2005) himself a sufferer, has described as a 'polymorphic collection of chronic, enduring, and in some cases disabling symptoms'. Murphy ea (2008) found that UK soldiers who remembered getting multiple vaccinations before going to the Gulf had multiple physical symptoms but that this did not tally with actual recorded number of vaccinations, i.e. there was recall bias. Thomas ea, (2006) in a systematic review, found that deployment in the Gulf was strongly associated with chronic fatigue syndrome and, to a lesser extent, with multiple chemical sensitivity or chronic multi-symptom illness. As the number of soldiers available for deployment fall duration of deployment increases as does PTSD, GHQ caseness, and multiple physical complaints. (Rona ea, 2007) It therefore seems wise to reduce duration of deployment as much as possible. Iversen ea (2008) suggest that the psychological impact of deployment might be lessened by factors such as good unit morale, leadership, and preparation of soldiers for their role in war theatre.

It is important to bear in mind that psychotherapies with research-based efficacy for PTSD are not widely available. (Gilbertson ea, 2008, p. 476) *Debriefing does not work for everyone and it has the potential to some cases worse, especially if it is used too early.* Debriefing remains a controversial subject with arguments for and against. (Wessely & Deahl, 2003; Sijbrandij, 2006) In a meta-analysis, van Emmerik ea (2002) found that single session critical incident stress debriefing (CISD) and non-CISD interventions did not improve on natural recovery from psychological trauma. Brief-series CBT started 2-4 weeks after impact in high-risk cases may have efficacy (Litz ea, 2002), a finding supported by meta-analysis. (Roberts ea, 2009) Gist & Devilly (2002) are highly critical of debriefing. They find that PTSD criteria for stressor and duration have broadened to include non-traumatic cases, that we really know little about the variable courses and outcomes among individuals who have been traumatised, and that debriefing has been taken

¹⁷⁰⁸ The Japanese, who value the group over individual autonomy, may fear that their activity (blushing, eye-to-eye contact, body odour, etc) will offend others (*Taijin kyoufusho*).

over by the poorly informed. Single session CBT has been used with effect to treat earthquake survivors, as has behavioural intervention with an earthquake simulator. (Basoglu, 2004) Brief CBT may speed up relief of symptoms of acute PTSD without affecting long-term outcome. (Sijbrandij ea, 2007) Cognitive therapy was effective for PTSD related to terrorism and other civil conflict in Northern Ireland. (Duffy ea, 2007) Excessive fear responses to fear-eliciting stimuli¹⁷⁰⁹ may be important in limiting response to CBT. (Bryant ea, 2008a)

The Royal Air Force offers more than simple debriefing, e.g. prolonged residential introduction and group integration, problem-solving training, involvement of the family, and a year long follow-up. Treatment embraces the various forms of psychotherapy. Flooding in imagination has been employed. Flooding was deemed to be better than counselling by Vietnam War veterans.¹⁷¹⁰ Image habituation training involves the patient listening to his audiotaped description of a traumatic event.

A self-help booklet failed to help trauma victims in a study by Turpin ea. (2005)

Antidepressants are useful in about 70% of cases and serotonergic agents may have an advantage. Symptoms such as recurrent, distressing recollections or nightmares may respond¹⁷¹¹ better to TCAs or SSRIs whereas symptoms like avoidance, lack of interest, or restricted affect require psychotherapy and, perhaps, SSRIs. According to some sources, phenelzine is useful for combat PTSD whereas fluoxetine is good for non-combatant PTSD but is ineffective for combat PTSD. Fluoxetine, in doses of up to 60 mgs./day, has been shown to be superior to placebo in civilians with PTSD. Fluoxetine reduces PTSD symptoms and prevents relapse for at least the first 6 months of treatment. (Martenyi ea, 2002) A systematic review and meta-analysis (Mooney ea, 2004) supports the use of sertraline for PTSD. Alprazolam is no better than placebo in reducing symptoms of PTSD; in fact, benzodiazepines may exacerbate PTSD or increase the likelihood of its occurrence. (Gelpin ea, 1996) Venlafaxine was effective and well tolerated in a 6-month randomised controlled trial (Davidson ea, 2006) and mirtazapine was as efficacious as sertraline in another randomised, controlled trial. (Chung ea, 2004)

NMDA channel and specific peptide receptor blocking agents inhibit the physiological and behavioural corollaries of PTSD in animals. The NMDA receptor or the beta-adrenoreceptor¹⁷¹² may prove suitable drug targets in humans. It has been suggested that drug treatment in PTSD may be too late to prevent brain traces underlying the disorder being laid down, but that reactivation of memories followed quickly by drug therapy may be helpful. How much damage to other memories would follow such controversial interventions is unknown. (Morrison ea, 2002)

Eye-movement desensitisation and reprocessing¹⁷¹³ (EMDR)

Therapy for PTSD (Coetzee & Regel, 2005)

Patient mentally visualises image of traumatic event

While he thinks of some phrase which represents how he feels about it (e.g. 'have no control'), bilateral saccadic eye movements are induced by following the therapist's rapidly moving (side to side across visual field) index finger (held about 35 cm from patient's face: 2 waves/second for total of 24 waves)

An important part of the procedure is replacing the negative belief statement with a preferred one, such as 'I have control'

While the patient repeats this statement to himself, saccadic eye movements are again induced

This 're-processing' procedure is repeated for all memories which are causing anxiety, until no anxiety is evident

It is unclear how essential are the eye movements (e.g. Seidler & Wagner, 2006)

EMDR may be no more effective than exposure therapy (e.g. Taylor ea, 2003) or trauma-focused CBT (Seidler & Wagner, 2006)

¹⁷⁰⁹ The authors used fearful and neutral faces to elicit responses in 14 PTSD cases. Treatment was with CBT. Imaging was with fMRI. Amygdala and ventral anterior cingulate activation predicted treatment response to cognitive behaviour therapy.

¹⁷¹⁰ Flooding, however, has generally become less popular as a treatment because of the intense discomfort associated with it.

¹⁷¹¹ The alpha-1 adrenergic antagonist prazosin may help for PTSD-related nightmares.

¹⁷¹² In one study of cardiac surgery cases (Krauseneck ea, 2010) adrenaline (beta-stimulation) enhanced memory for adverse experiences in men but not women whereas the beta-blocking drug metoprolol decreased memory for post-operative adverse events and PTSD symptoms in females only.

¹⁷¹³ Francine Shapiro PhD (Palo Alto, California) noticed that whilst looking intently at tree leaves moving in the wind one's mind turns from unpleasant thoughts.

EMDR and trauma-focused CBT are first-line psychological therapies for PTSD according to systematic review (Bisson ea, 2007a)

Most positive studies are flawed and value is unclear (Marshall ea, 2008, p. 605)

Ten daily sessions of repetitive transcranial magnetic stimulation (rTMS) applied over the right dorsolateral prefrontal cortex at a frequency of 10 Hz may help some patients.(Cohen ea, 2004)

A flexible, client-centred approach is likely to give the best results. According to Bowman,(1999) evidence from a number of studies suggests that an approach aimed at solving problems may be superior to one based on emotional display.

Disaster management – some principles (after Bisson ea, 2007b)

Have an agreed plan that includes psychosocial intervention

Non-mental health professionals:

Supply emotional support and information

Verbal and written information on normal responses and their tendency to subside over the short term

Advice to avoid excess drugs and alcohol

Avoid structured interventions

Do not force ventilation of feelings but listen to those who wish to ventilate

Advice to contact GP if symptoms persistent or severe

Mental health professionals:

Co-ordinate response

Support and supervision of non-mental health professionals

Deal with complicated cases, e.g. overwhelming anxiety or psychosis

About 30-50% of PTSD cases recover within 12 months.(e.g. Yule ea, 2000) Up to a third still have PTSD even many years later.(Kessler ea, 1995) Strong social supports, adherence with treatment, use of evidence-based treatments, and no comorbid disorders suggest a good outlook, the opposite being suggested by social isolation, drug abuse, poor cognitive ability, and many childhood traumas.

Management of torture victims¹⁷¹⁴

Physicians should not be directly or indirectly (advice, monitoring, etc) involved in torture (Marks, 2008)

Integrated, flexible, client-centred approach using a variety of techniques

Help patient feel accepted

Acknowledged fact that torture occurred

Security for the self and for friends left behind

Psychiatric help, e.g. treating depression

Help with psychological working through

Retelling the story of the trauma may be used to create a statement of testimony against torture

Cognitive-behavioural strategies, marital or family therapy to reduce the impact on relatives

Techniques to increase social support and reduce post-captivity depression and anxiety

Prior knowledge of what to expect, strong commitment to a cause, immunisation as a result of repeated exposure, and strong social supports may protect against PTSD in torture survivors

Physical therapies, e.g. analgesics for pain (see Mayou & Bryant, 2002)

Phobias

¹⁷¹⁴ There has in practice been little progress in impacting the suffering of **torture** victims.(Başoğlu, 2007) Torture in forms other than physical (psychological manipulation, humiliation, forced stress positions) causes just as much suffering and similar mental outcomes to classic torture.(Başoğlu ea, 2007) Traumatic head injury (prefrontal and temporal) in Vietnamese ex-political detainees was found to be associated severity of depression.(Mollica ea, 2009) Unfortunately, medical professionals have been (e.g. Nazi Germany, Guantanamo Bay) and still are involved in what amounts to torture in some parts of the world (genital mutilation, testing for homosexual activity or virginity, and withholding treatments for 'self-induced' problems).(Anonymous, 2010)

A phobia must fulfil the following criteria: a fear that is out of proportion to the stimulus; involuntary; refractory to logical argument; and leads to avoidance of the feared stimulus. The aetiology of phobias are most likely complex and different factors may weigh differently in their contribution to individual cases. (Ollendick et al., 2004) Research in twins suggests that the fear conditioning process is moderately heritable, in the 35-45% range. (Hettema et al., 2003) It may be that people who inherit a worrying or autonomically reactive temperament may be prone to develop phobic disorders. (Ollendick et al., 2004) Psychoanalysts explain phobias as resulting from unresolved childhood conflicts, with displacement and avoidance as defences against castration anxiety. Put another way, the phobic situation is a symbolic representation of an inner conflict that the sufferer wants to avoid, the anxiety being displaced from the conflict onto a more readily available external object or situation. Phobias may start by the pairing of fear with a stimulus (Pavlov's classical conditioning) and be maintained by the reduction in anxiety associated with the avoidance of the same stimulus (Skinner's operant conditioning)¹⁷¹⁵. Other possibilities are the observation of others showing fear in the presence of an object or situation or being informed that such things should provoke fear by the media. Rachman (1977) suggested three pathways to fear acquisition: direct classical conditioning, vicarious conditioning (seeing others show fear), and information/instruction (being told fear-inducing stories).

Another putative mechanism is 'preparedness' or 'prepotency', i.e. things that were dangerous for our primitive ancestors, such as heights, are more likely to lead to phobias than are relatively harmless objects such as flowers. (Marks, 1969) The most successful exposure therapies for phobic disorders tend to be prolonged, given in a real life setting, and are regularly practiced with self-exposure homework tasks. (Stern, 1998)

People with phobic disorders are much less likely to seek help than, say, people with panic disorder. (Kessler & Walters, 1998) There are three major groups of phobia:

Specific (simple) phobia. An example is the fear of various animals such as furry animals¹⁷¹⁶ or spiders. Early during the twentieth century, Watson and Rayner (1920) induced animal phobia in a boy using classical conditioning. The kind of things we become phobic for (e.g. heights) and those that we do not develop phobias for (e.g. motor cars) suggests a survival function among our ancient ancestors. Genetic input into specific phobia appears to work mainly via temperamental inhibition (shyness). In practice, whilst some people relate experiencing an unpleasant event to which they attribute their phobia, this is by no means universally true.

Specific phobia

Usually starts in childhood, but can commence later (usually following a stressful event)

Adult onset cases have a better prognosis than do cases persisting from childhood

Among adults, the DSM-III-R lifetime prevalence rate has been estimated as 13% for women and 4% for men (Simonoff et al., 1997)

Virginia twin study (8-16 year olds) reported prevalences (per 1000) of 212 and 108 for specific phobia and overanxious disorder respectively; 21% were functionally impaired, contrasting with overanxious disorder (41%) and major depression (93%); Functional impairment was associated with comorbidity

National Epidemiologic Survey on Alcohol and Related Conditions (Stinson et al., 2007): 12-month and lifetime prevalences of DSM-IV specific phobia were 7.1% and 9.4% respectively; mean onset at 9.7 years; mean episode duration of 20.1 years; 8% received specific treatment; mostly multiple fears, and the more fears the greater disability, treatment seeking and comorbidity (axes I and II)

There is a good outlook, at least in the short term¹⁷¹⁷, with behaviour therapy. Modelling involves the therapist in demonstrating the lack of real danger in performing some act. Severe cases may persist into adult life.

¹⁷¹⁵ This idea stems from the American psychologist Orval Hobart Mowrer (1907-82).

¹⁷¹⁶ May generalise to include any furry or soft object.

¹⁷¹⁷ A 10-18 year follow up of 28 people who were treated for specific phobia found that 40% had clinically significant symptoms whilst 62% of 'responders' were practicing avoidance or suffering whilst continuing to expose themselves to dreaded stimuli. (Lipsitz et al., 1999)

Needle phobia is seen in people subjected to repeated venepuncture or hypodermic injections. Blood-injection-injury phobia (Page, 1994) encompasses a wider array of fears than needle phobia: injections, mutilation, medical equipment, etc. Patients may avoid essential procedures. They faint if exposed to blood or injury; there is a biphasic response with hypertension and tachycardia followed by hypotension and bradycardia, i.e. vasovagal syncope. Management includes exposure or graded desensitisation (lying down at first). The patient can be taught *applied tension*: tense the hands and arms before and during exposure to prevent hypotension (it is the exposure that is therapeutic). (Öst & Sterner, 1987)

Phobia for chemotherapy or radiotherapy is a conditioned response in which anticipatory anxiety and nausea and vomiting leads to treatment avoidance. It has been treated with antiemetics¹⁷¹⁸, short term BZDs, and systematic desensitisation.

<i>Examples of names for phobias</i>

¹⁷¹⁸ E.g. the 5-HT₃ antagonists ondansetron and granisetron.

Acro-phobia (a fear of) heights
 Agora- open places
 Ailuro- cats
 Algo- pain
 Amatho- dust
 Astra- thunder and lightning (syn. Bronto-)
 Aviato-, flying^
 Claustro- confined spaces*
 Coito- sexual intercourse
 Cyno- cats (syn. Felino-)
 Dento- dentists
 Entomo- insects (Api-, of bees; Arachno-, of spiders; Motte-, moths)
 Frigo- cold weather
 Hoplo- , firearms
 Iatro- doctors
 Kerauno- thunder
 Myso- dirt
 Nebula- fog
 Noso- disease/suffering**
 Nycto- night/dark***
 Odyne- pain
 Ophidio- snakes
 Phono- loud voices
 Pyro- fire
 Tapho- being buried alive
 Toko- a morbid fear of childbirth in a woman, despite a wish to have a baby
 Topo- stage fright
 Triskaideka- number 13
 Trypano-, injections
 Xeno- strangers

^ see <http://www.fearofflyinghelp.com>. *Marks and Mataix-Cols (2004) refer to the agoraphobic cluster of situations, e.g. shopping, leaving home alone, etc. This may include claustrophobia. However, if claustrophobia is the single fear, these authors would classify it as a specific phobia. 'The more situations that are feared from the agoraphobic cluster, the more the problem can be called agoraphobic'. In other words, these categories are artificial with 'no sharp dividing line'. **Marks and Mataix-Cols (2004) suggests that worrying about one illness constitutes a specific illness phobia; if the fear is of many illnesses the diagnosis is hypochondriasis; the authors do admit that boundaries are not always clear. ***Achluophobia refers specifically to fear of darkness.

Social phobia. ('wall-flower' of the dancehall; social anxiety disorder) This is not mere shyness.(Stein & Stein, 2008) Social phobia is characterised by fear of being scrutinised by others, a fear of what others may think. We often feel some level of anxiety on social occasions, but the socially phobic experiences such a high degree of anxiety as to disrupt their lives. Sufferers may fear being tremulous, sweaty, blushing, vomiting in public, looking stupid, etc. Life becomes restricted, as when the person only ventures outdoors in darkness. People with this problem may avoid consultation because they do not view it as an illness or because they fear what the professional may think about them. This disabling and underdiagnosed condition has a mean age of onset in the mid-teens or earlier¹⁷¹⁹. It may affect up to 10% of people; the one year prevalence in the US has been estimated as 9% for women and 7% for men. Subthreshold cases that fail to meet diagnostic criteria are very common. Lifetime prevalence rates vary from 2.4-16%. The National Comorbidity Survey (Kessler ea, 1994) estimated lifetime and twelve-month prevalences of social anxiety disorder at over 13% and 7.6% respectively (12.1% and 7.1% respectively in a replication study: Ruscio ea, 2008). The only commoner psychiatric disorders were major depression and alcohol abuse/dependence. Social phobia is often divided into generalised/diffuse (2 out of 3 cases) and specific/focal¹⁷²⁰ types, the former being more severe and potentially disabling.(Kessler ea, 1998) It has been suggested that public-speaking fears should be included with the social phobias. This generally comes on in the teens, but later onset, in the present author's experience, should prompt a search for some other disorder, such as depression.

According to Marks and Mataix-Cols,(2004) marked shyness in childhood may persist into adulthood but most focal social phobias commence in young adulthood. 'Shy bladder syndrome'¹⁷²¹ and fear of speaking

¹⁷¹⁹ 50% onset by age 11 years and 80% onset by age 20 years.(Stein & Stein, 2008)

¹⁷²⁰ Circumscribed fears such as public speaking or urination.

¹⁷²¹ Fear of urinating in a public toilet.

to a date may also be included among the phobias. Fear of urinating/defecating in public toilets or of being incontinent when a toilet is not available are sometimes called 'sphincteric phobia'. Marks and Mataix-Cols (2004) point out that sphincteric phobias are free of other social phobias.

There is an increased risk for later depression and alcoholism/substance abuse.(Stein & Stein, 2008) Akiskal and Perugi (2004) argued for an association between bipolar affective disorder and social phobia, arguing that social phobia usually precedes hypomanic episodes and disappears when the hypomania supervenes. However, this 'social phobia' could be a manifestation of depression in bipolar II disorder. Functional neuroimaging suggests increased activity in amygdala and insula in social phobia.(Stein & Stein, 2008)

Social phobia (social anxiety disorder)¹⁷²² must be distinguished from:

Separation anxiety

GAD

PTSD - avoidance based on trauma

Specific phobia

Panic disorder with agoraphobia - fear of having a panic attack

OCD - avoidance related to, say, dirt/contamination

Performance anxiety

Social inadequacy with shyness

Avoidant¹⁷²³ and schizoid personality disorders

Schizophrenia - avoidance based on delusions

Similar symptoms in depression - may outlast depression for some time

Parental psychopathology (especially social phobia and depression) and perceived parental style (overprotection or rejection) seem to be associated with the development of social phobia in offspring.(see Knappe ea, 2008) Social phobia seems to be more common in close relatives of autistic children and in girls with fragile X syndrome.(Oosterheld ea, 2003, p. 335) Dopamine may be involved in social phobia because mice bred to be timid have a low dopamine brain concentration.

A PET study (Furmark ea, 2004) found that patients with social phobia who possessed 1 or 2 copies of short allele of the 5-HTT gene had much greater trait and state anxiety and increased right amygdala activation while speaking publically compared with socially phobic patients who were homozygous for the long allele. In one study (Goldin ea, 2009), compared to controls, patients with social anxiety disorder had exaggerated negative emotional reactions and reduced neural activity related to cognitive regulation on fMRI following socially threatening stimuli.

Treatment may be ineffective for 30-40% of cases.(Stein & Stein, 2008) While psychological treatments help adults with social anxiety disorder they may not be particularly effective in more severe cases (meeting DSM criteria) and in studies that used placebo or usual care rather than waiting list controls!(Acarturk ea, 2009) Systematic desensitisation is not very effective. Exposure¹⁷²⁴, social skills training (SST: the evidence for SST is mixed: Ponniah & Hollon, 2008) and cognitive therapy may be offered as a package. Exposure, if tolerated and completed, has long lasting benefit. Assertiveness training may be tried. Role-playing may be of benefit in social phobias, and this might include, for example, talking to an opposite-sexed partner on a date. CBT (exposure and anxiety management) appears to be superior to both placebo and to exposure alone, but perhaps inferior to phenelzine in terms of quality of response (but patients are more likely to relapse when the drug is stopped than when CBT ceases). Exposure has been seen as the key component of CBT in this disorder (Barlow ea, 2004, p. 190; Ponniah & Hollon, 2008) but the whole CBT package may be best.(Hofmann, 2004) MAOIs are effective¹⁷²⁵, as are venlafaxine¹⁷²⁶, the

¹⁷²² Fear of being judged by others and/or embarrassing oneself in public.

¹⁷²³ Some authorities, such as Marks and Mataix-Cols,(2004, p. 22) and Torres (2005) equate this with social phobia and some see it as commonly comorbid with social phobia, others such as Rettew (2000) place avoidant personality disorder, generalised social phobia, and shyness on a continuum. According to Reichborn-Kjennerud ea (2007), a common genetic vulnerability underlies both disorders in female twin pairs with differing life events determining final expression (common environmental effects could not be ruled out).

¹⁷²⁴ Extinction is blocked by by antagonism of the NMDA receptor and D-cycloserine (given an hour before exposure), a partial agonist at this receptor, facilitates extinction of conditioned fear.(Campbell-Sills & Stein, 2008, p. 568)

¹⁷²⁵ Phenelzine plus CBT group therapy was better than placebo and either treatment on its own in one RCT.(Blanco ea, 2010)

SSRIs paroxetine (Stein ea, 2002), fluoxetine,(Davidson ea, 2004), escitalopram (Kasper ea, 2005) and the other SSRIs as well. An adequate SSRI trial is at least three months and relapse is a significant risk if responsive patients are switched to placebo. Whether moclobemide (Manerix) is effective has been strongly debated.(Hollander & Simeon, 2003, p. 577; Cowen, 2005) There is some evidence for efficacy with mirtazepine and for Pregabalin. Beta-blockers are ineffective for generalised social anxiety¹⁷²⁷. BZDs, especially clonazepam, give relief but carry their own problems and are less effective than the SSRIs. Venlafaxine,(Kelsey, 1995) bupropion, and gabapentin may be worth trying in resistant cases. Many patients remain symptomatic despite treatment responses that are superior to placebo.(Davidson ea, 2004) Alcohol, despite common belief, is no better than placebo for social anxiety¹⁷²⁸; however, a person who mistakenly thinks that he imbibed alcohol might experience relief!(Himle ea, 1999)

Agoraphobia.¹⁷²⁹ This affects young women in particular, who may become house bound¹⁷³⁰. If patients venture out, they will bring a friend, a spouse, or a dog. They are poor clinic attenders. DSM-III-R one-year prevalence has been reported as 3.8% for women and 1.7% for men. There is a normal class and education distribution. The partner or the child¹⁷³¹ may be kept at home as well. It may start as a panic attack in the street, in church, or in a supermarket. Psychoanalysts have explained agoraphobia as stemming from early maternal deprivation or traumatic separations in early life. It is often chronic and subject to exacerbations. McGennis ea (1977) divided agoraphobia into primary ('an abnormal fear of going out unaccompanied') and secondary (depression or schizophrenia) cases. However, the core fear may be of being separated from a source of security. Some authors stress the fear of a second panic attack leading to agoraphobic behaviour and write that agoraphobia without a history of panic disorder is very rare in clinical practice. Each case should be subjected to careful assessment with collateral information gathering. Brief episodes of depression during the course of chronic agoraphobia may prompt a visit to the doctor.

'Out and About'¹⁷³² is a national self-help association for Irish agoraphobics. Behaviour therapy is effective for specific phobias. Desensitisation (i.e. systematic desensitisation) involves gradual increases in exposure to the feared stimulus. Flooding involves sudden and sustained exposure. Ghosh ea (1988) found that, when treating phobias, self-exposure (to the feared stimulus) treatment was equally effective if a psychiatrist, a computer, or a book was used by the patient, and all held the same effect at six-months follow-up.

Serotonin-reuptake inhibitors (SRIs) such as clomipramine and the SSRIs are the drug treatments of choice, although other antidepressants (MAOIs, SNRIs, TCAs, reboxetine) and benzodiazepines (clonazepam, alprazolam) may help individual cases.(Schatzberg ea, 2005, p. 23)

It may have the worst prognosis among the phobias. It may be complicated by drug or alcohol abuse.¹⁷³³

Space phobia is a fear of falling made worse by the absence of any immediate source of support and is especially common in open spaces. It has a later age of onset than agoraphobia, with a mean onset at 55 years of age, and it does not respond to behaviour therapy. It is often accompanied by evidence of neurological or cardiovascular disorder.

Chronic fatigue syndrome¹⁷³⁴ (CFS)

This is an idiopathic disorder (Prins ea, 2006; Baker & Shaw, 2007) that affects women more than men.(Evengård ea, 2005; Sullivan ea, 2005a)

CFS was said to be uncommon in children (Chalder ea, 2003) but Farmer ea (2004) found that children aged more than eleven years might not differ significantly from adults in terms of prevalence, symptoms, gender distribution, severity and comorbid depression.¹⁷³⁵ Crawley ea (2009) found that separation anxiety and social phobia were prominent in paediatric CFS.

¹⁷²⁶ Lower doses may be as effective as higher doses.(Campbell-Sills & Stein, 2008, p. 569)

¹⁷²⁷ However, beta-blockers like atenolol decrease performance anxiety in normal people.

¹⁷²⁸ Or anxiety symptoms in general for that matter.

¹⁷²⁹ 'Fear of the market place'. Westphal originally defined agoraphobia in 1872.

¹⁷³⁰ Initially being housebound may be a source of annoyance to a partner. However, the housebound person may take on extra household chores so that the rest of the household becomes discommoded when treatment is aimed at helping the patient break out of this mould.

¹⁷³¹ Part of the differential diagnosis of school refusal.

¹⁷³² St. John's House, Seafield Road, Clontarf, Dublin 3. Founded by Mortimer Murrhly, a psychiatric nurse, in May 1974.

¹⁷³³ The present author's experience has taught him that secret alcoholism can sometimes present as agoraphobia.

¹⁷³⁴ Epidemic neuromyasthenia, myalgic encephalomyelitis (ME), Royal Free Hospital disease, Iceland disease, Yuppie flu.

¹⁷³⁵ However, the latter study was conducted over the telephone with parents and there was a problem with validating the interview questions.

CFS is probably not as new as its modern names suggest. Doctors dislike self-diagnosis among their patients, a practice that may be encouraged by groups for ME patients as well as Internet sites.(Page & Wessely, 2007, p. 138) The diagnosis is less common in primary care in Brazil than in Britain but Brazilian doctors are just as likely as their British colleagues to record the symptoms of CFS.(Cho ea, 2009) It serves no purpose to disbelieve what is often a very handicapped patient.(White ea, 2007)

Risk factors for CFS have still to find application in clinical practice.(Hempel ea, 2008) Very few patients who complain of 'fatigue' in primary care settings are referred to hospital specialists. Most people with chronic fatigue do not have CFS. The criteria for CFS are wider¹⁷³⁶ than the original ME criteria. Some authors have suggested that CFS is more or less identical with neurasthenia¹⁷³⁷, is culturally sanctioned, will disappear like neurasthenia, and may be better classified under some other psychiatric label or as a psychophysiological reaction. Sullivan ea (2005b) obtained data from twins by telephone and concluded that CFS is a complex trait resulting from both environmental and genetic sources. Harvey ea (2008) found that people with psychiatric illness between the ages of 15 and 36 years had an increased likelihood of later reporting CFS and depression and anxiety in particular were common before CFS. Roy-Byrne ea (2002), using data from a highly selected small twin sample, suggest that chronic fatigue may more closely resemble atypical, anxious forms of depression than 'classic' depression. CFS patients do better than major depressives and worse than healthy controls on cognitive tests and their maximum voluntary contraction improves less than that of than major depressives during the day whereas the strength of contraction in the depressives improves more than in healthy controls.(Lawrie ea, 2000) Others wonder if it is primarily a sleep-related problem. Other workers have found CFS patients to be fitter than controls,(Bazelmans ea, 2001) although Viner and Hotopf (2004) found that sedentary behaviour increases the risk for CSF. Like CFS patients themselves, the partners of these patients are more likely to see the symptoms as having a somatic basis.(Butler ea, 2001) The commonest reason given by lay people for this complaint is a psychosocial problem, only a small minority (1.4% in one English sample) attributing it (excessive tiredness) to CFS.(Pawlikowska ea, 1994) Fatigue is distributed as a continuous variable in the community. Indian women with chronic fatigue were found to have an excess of poor mental health and gender disadvantage, notably sexual violence by the husband.(Patel ea, 2005)

A population-based study (Heim ea, 2006, 2009) found an excess of self-reported childhood adversity (sexual, physical, and emotional abuse as well as emotional and physical neglect) in cases of CFS; such adversity was also associated with more severe CFS and with symptoms of depression, anxiety, and PTSD; also, patients with a history of such childhood trauma, but not those lacking such a history, have decreased salivary cortisol after awakening. A prospective study (Kato ea, 2006) found that premorbid stress was a risk factor for CSF, as was emotional instability assessed 25 years earlier; genetic factors appeared to influence the effects of these predictors. Excess life events, particularly the dilemma of having to choose between undesirable options, are reported in a minority of cases before the onset of CFS.(Hatcher & House, 2003)

An estimated prevalence¹⁷³⁸ of 0.04% of the Australian population had CFS in 1990, women slightly outnumbering men, and with a mean age of onset of about 39 years. In general, estimates of prevalence tend to range from 0.3% to 1.5%. There may be little pathological basis for calling it an encephalomyelitis or a myopathy. It has been suggested that patients might have an abnormal perception of effort. Fatigue before an infection tends to be associated with post-infection fatigue. Indeed, a study in primary care found that people who complained of fatigue for more than six months following an infection were more likely to be fatigued prior to the infection.(Wessely ea, 1995)

Symptoms are chronic, and non-specific, and include fatigue, weakness, myalgia, memory loss and concentration difficulties¹⁷³⁹, and depression. Patients may be severely incapacitated, often missing school or work. Some take to wheelchairs. Laboratory findings, including CSF, are normal.

¹⁷³⁶ With 'hazy' boundaries.(Musser & Schiffer, 2003, p. 1196)

¹⁷³⁷ Others suggest that most cases of neurasthenia suffer from anxiety or depression. Neurasthenia, known in China as *shenjing shuairuo*, has become a less popular diagnosis, particularly in urban areas, and the Chinese classification system of mental disorders (CCMD-3) describes it as a diagnosis of exclusion.(Lee, 2001)

¹⁷³⁸ There were 'outbreaks' in a Los Angeles hospital in 1934 of 'epidemic neuromyasthenia' (paralysis) and at London's Royal Free Hospital in 1955.

¹⁷³⁹ **Cognition in CFS:** Dickson ea (2009), on the basis of a study comparing healthy people and patients with autoimmune thyroid disease with CFS sufferers, suggest that impaired attention may be a primary cognitive problem in CFS. Cockshell and Mathias (2010) performed a meta-analysis and found mainly problems with attention, memory, and reaction time.

Fatigue states can follow infectious disorders (postviral fatigue syndrome¹⁷⁴⁰), such as infectious mononucleosis, and physical and psychiatric disorders often co-exist. It has been that CFS is due to chronic cytokine (e.g. interferon) release from lymphocytes during viral infection. Coxsackie B and Epstein-Barr viruses do not seem responsible for CFS. There has been a report of enteroviral RNA in muscle biopsy specimens in postviral fatigue. Lombardi ea (2009) detected a retrovirus, XMRV, in the blood cells of a significant proportion of patients with CFS¹⁷⁴¹ but this finding has since been refuted in a number of studies.(McClure & Wessely, 2010) Chia and Chia (2007)¹⁷⁴² state that most CFS cases have persistent or intermittent GIT symptoms and that on gastric biopsy they viral capsid protein 1 (VP1) in 82% and 20% of CFS patient and control parietal cells respectively, suggesting chronic enterovirus infection of the stomach. Lyme disease can cause fatigue. The widely held belief that antibiotics cause fatigue was not upheld in a double blind, randomised crossover trial in healthy volunteers of amoxicillin v placebo.(Bergmann ea, 1993) MRI and standardised cognitive tests failed to support an organic aetiology (e.g. postviral) for CFS in a study by Cope ea.(1995)

Okada ea (2004), in a voxel-based morphometric study of CFS, found bilateral reduction in prefrontal cortical grey matter volume, the decrease correlating with fatigue.

Suggestions of increased brain serotonin levels are difficult to interpret; they could be primary or due to prolonged inactivity, disturbed sleep pattern, or some other variable; there is some evidence for increased activity of presynaptic 5-HT neurones. These observations, as well as suggestions of reduced hypothalamic-pituitary-adrenal axis function or reduced baseline cortisol levels, could be causing CSF or resulting from CSF.(Parker ea, 2001) Van Den Eede et al (2008) reported reduced cortisol responses in the combined dexamethasone/CRF test in CFS cases *without* a history of early-life stress. Cortisol levels return to normal following behavioural intervention.(Cleare, 2003)

In a neurological hospital, Wessely and Powell (1989) found major depression in half of cases of chronic postviral fatigue, no psychiatric disorder in almost a quarter, somatisation in 13%, minor depression in 6%, anxiety disorder in 4%, phobia in 2%, and conversion disorder in 2%.

Among patients attending an infectious diseases clinic with idiopathic fatigue, many improve spontaneously but functional impairment is associated with belief in a viral cause, reduction in exercise, avoidance of alcohol, a change in job, quitting work, belonging to a self-help group, or having a current emotional disorder on follow up.(Sharpe ea, 1992) Of course, these characteristics could denote consequences or aetiological contributions to fatigue. Darbishire ea (2005) found that meeting the criteria for CFS was the most powerful predictor of poor outcome. A shorter history of fatigue and an absent history of anxiety or depression may favour a better prognosis for CFS, as may the absence of a primary psychiatric diagnosis at follow up or the lack of a belief in the explanatory power of a physical diathesis for ones symptoms. Diagnostic uncertainty on the part of the physician and the provision of a sick note may be unwitting contributors to an adverse outcome. Most patients get better¹⁷⁴³ but a significant minority is functionally impaired. Psychological factors are more important predictors of outcome than immunological¹⁷⁴⁴ or demographic variables.(Wilson ea, 1994; Skapinakis ea, 2003) Bentall ea (2002) found a poor outcome in the psychological treatment of CFS to be associated with resistance to accepting therapeutic rationale, poor motivation to adhere to the treatment and secondary gains from illness. People in support groups, those currently emotionally distressed, receipt of sickness benefits and an exclusive belief in a physical aetiology were associated with adverse outcomes.

Various treatments have enjoyed transient period of popularity such as magnesium supplementation. Iron supplementation for unexplained fatigue in the absence of anaemia only seems beneficial if the patient has low or borderline serum ferritin concentration.(Verdon ea, 2003) Controlled trials of antidepressants have been disappointing, although some cases are helped. The anticholinergic side effects of TCAs may be difficult to tolerate. Low doses of TCAs may however alleviate insomnia and pain. SSRIs only help if the patient is depressed. Mirtazapine following CBT was found helpful by Stubhaug ea.(2008) Doctors should

¹⁷⁴⁰ An Australian study (Hickie ea, 2006) found that post-infective fatigue (disabling tiredness, musculoskeletal pain, neurocognitive problems, and disturbed mood) was largely predicted by severity of acute illness and not by demography, psychology, or microbiology.

¹⁷⁴¹ Retroviruses include HIV. XMRV = xenotropic murine leukemia virus.

¹⁷⁴² Chia JK-S, Chia AY. 'Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach'. *J Clin Pathology* September 2007: <http://press.psprings.co.uk/jcp/september/cp50054.pdf>.

¹⁷⁴³ Including CFS children when followed to adulthood.

¹⁷⁴⁴ Lyall ea (2003) could find no consistent evidence for an immune disorder in CFS in their systematic review.

encourage 'fatigued' patients to deal with their psychosocial problems and discourage prolonged rest. Wessely ea (1988) reported an improvement in myalgic encephalomyelitis using a combination of cognitive-behavioural methods and graded exercise. They suggested that instead of resting after influenza one should start taking regular gentle exercises to get going again. Brief courses of graded exercise therapy may be inadequate.(Ridsdale ea, 2004)

An effective treatment package might consist of CBT¹⁷⁴⁵, (Stulemeijer ea, 2005) reassurance that the disorder is non-organic¹⁷⁴⁶, a diagnosis of CFS, and advice to increase activity levels in a graded manner.(McCrone ea, 2004) Graded rehabilitative exercises should be based on present and not past ability. These should be started without delay.(Powell ea, 2004)

Smith ea (2006) found no excess for all-cause mortality or suicide in a cohort of CFS cases.

Neuroses: general considerations

Those without personality disorder may be more likely to respond to psychological treatment methods, whereas those with personality disorder may respond better to medication, particularly antidepressants. However, the literature has not been uniform in this regard.

Neurotic states are relatively common in the elderly. They are often not seen by doctors and may be missed or misdiagnosed, or simply put down to advanced age or somatic illness. Alternatively somatic disorders may be misclassified as neuroticism. The clinical picture may be complicated by alcohol abuse or by dependence on or side effects from therapeutic drugs. Hysterical disorders may arise as a result of missed physical illness or they may be due to the release of dissociative tendencies in vulnerable people by organic brain disease or functional psychiatric illnesses.(Lindesay, 1997)

Recovered memories

The 'false memory syndrome' implies that people falsely recall being victims of CSA because it is has been suggested to them that it did occur. Some patients 'recall' murders. Many experts doubt the possibility that one can develop dissociative amnesia for traumatic events and warn us to outrule organic causes like head injury or intoxication. Various forms of backlash against 'recovered memories' have occurred on both sides of the Atlantic, both by those who say they have been falsely accused by these recollections and by insurance companies who refuse to pay therapists who harvest them.(O'Shea, 2000a)

Factitious disorders

Factitious disorders have probably always been with us and they occur throughout the globe.(McDermott ea, 2008, p. 643) It took years before Munchausen syndrome ceased to be viewed in a purely exotic medico-surgical way instead of the psychosocial problem it represents.(O'Shea a, 1984; O'Shea, 2003; Eisendrath & Young, 2005)¹⁷⁴⁷ These patients repeatedly seek admission to hospital with plausible but consciously faked or exaggerated histories to support complaints of a physical or psychiatric nature. They submit to potentially hazardous investigations and treatments, and discharge themselves against medical advice if challenged when tests or observation negate their complaints. Many cases over-reported and many are missed. Factitious disorder was diagnosed in 10 or 0.8% of 1,288 consecutive inpatient referrals in one Canadian hospital.(Sutherland & Rodin, 1990) In a Scottish 10-year study of thyrotoxic patients presenting to Edinburgh's Royal Infirmary, 0.2% of cases were diagnosed as factitious hyperthyroidism¹⁷⁴⁸.(Strachan & Walker, 2006, p. 746) Bhugra (1988) reported that 0.5% of psychiatric admissions had Munchausen's syndrome.

¹⁷⁴⁵ Unskilled practitioners may not deliver CBT effectively.(Huibers ea, 2004) Low cortisol levels may be associated with poor response to CBT in CFS.(Roberts ea, 2010)

¹⁷⁴⁶ Although a physiological 'explanation' often helps. Two patients challenged NICE Guidelines (CBT and graded exercise) in the High Court in London in 2009 stating that NICE should have used a biomedical model rather than a psychosocial approach. The challenge was rejected.(Dyer 2009)

¹⁷⁴⁷ Although such cases were known to doctors for many years,(e.g. Claudius Galen [c. 129 AD-c. 216 AD], Roman physician in Feldman, 2004, pp. 18-32; Gavin, 1838) Richard Asher (1912-69: see Turner & Reid, 2002) published his classic description of the presentation of the disorder with an emphasis on presenting physical signs in 1951. Galen wrote on feigned disease. Hector Gavin (1815-1855) was the first to use 'factitious disease'. He wrote about soldiers who mimicked of induced illness in themselves and women who 'assume the semblance of disease'. He belied the Irish were the best fabricators, followed the Lowland Scots! Gavin died of an accidental pistol wound in the abdomen in the Crimea.(Spriggs, 1984)

¹⁷⁴⁸ Exogenous T4 suppresses TSH as well as iodine uptake, serum thyroglobulin, and endogenous thyroid hormone release. In thyrotoxicosis the T4/T3 ratio is 30:1 but is > 70:1 in factitious cases. Negligible iodine uptake + high T4/T3 ratio + low/undetectable thyroglobulin = factitious.

The author recognises a *nuclear or classic factitious syndrome*¹⁷⁴⁹, more common in males, with extensive careers, costing an enormous amount of money to the exchequer over numerous admissions. The IQ, in this author's experience is often in the borderline range. *Non-nuclear cases* (90% of cases) may be more common in women who are mostly socially conforming, of a higher socioeconomic status than the peregrinating, alias-using nuclear group, and may be intelligent and educated, and are frequently employed in a medically related field. (Reich & Gottfried, 1983) *Munchausen/factitious disorder by proxy* (*frabricated/induced illness by carers, paediatric condition falsification, abnormal illness by proxy, vide infra*) perpetrators, on the other hand, are mostly female (Makar & Squier, 1990; Feldman & Eisendrath, 1996): Schreier and Libow (1993) could identify eleven reports out of nearly 200 where the father was the perpetrator. Mothers in such cases may give histories of insecure attachment in their own childhood. (Adshead & Bluglass, 2005)

The clinical features tend to include dramatic presentations, inconsistencies in their histories, complaint may be supported by congenital, static, or induced signs, there may be many operative scars, and almost any bodily system may be the focus of attention. The patient may be ingratiating and 'helpful' initially, profuse in thanks, but later becoming clinging and demanding. Staff may experience splitting due to identification and countertransference. An apparent high pain threshold may be accompanied by demands for opiate analgesia. Great ingenuity is shown in simulating illness. *Pseudologia phantastica* (pathological lying) refers to a free and effortless flow of lies that are immediately plausible. There is often a forensic history. The psychiatric subtype can include such varied complaints as PTSD following an non-existent military exploit or an exaggerated dependence on drugs. The F-K ('lie scale') on the MMPI is classically greatly elevated. Aetiology is obscure¹⁷⁵⁰ but there is evidence that it may stem from learning in childhood and may be continuous with MBP. However, pathological lying may be associated with a deficiency of prefrontal grey matter relative to prefrontal white matter. (Yang ea, 2005; Spence, 2005) The only pathognomonic sign is when the doctor sees the dye from last IVU leaving the bladder as dye from index IVU enters the kidney!¹⁷⁵¹

A high index of suspicion and knowledge of the profile described in bare outline above are required for a working diagnosis. Inexplicable laboratory results may prompt consideration of factitious disorder. (Krahn ea, 2003) Both ICD-10 and DSM-IV recognise absence of external incentives (economic gain, imprisonment, etc – malingering) in factitious disorders and motivation is *assumed* to be the adoption of the sick role. DSM-IV states that 'factitious disorders are distinguished from...malingering... (in that the malingerer) has a goal that is obviously recognisable when the environmental circumstances are known'. Criteria include intentional production or feigning of physical or psychological symptoms, motivation is to assume sick role, and external incentives are absent. Presentation can be 'predominantly psychological signs and symptoms', 'predominantly physical signs and symptoms', 'combined psychological and physical signs and symptoms', or 'factitious disorder not otherwise specified'¹⁷⁵². Modern examples of feigned disorders include factitious disorders include diarrhoea¹⁷⁵³, hypoglycaemia¹⁷⁵⁴, 'arrhythmias' produced by manipulating ECG leads, HIV/AIDS (Craven ea, 1994), Guillain-Barré syndrome, bereavement, amnesia (Doherty & Sheehan, 2010), psychosis, and altered electronic records. Patients may manipulate real treatments for real disorders, may have real plus feigned disorders, or may develop real disorders as a result of treatment¹⁷⁵⁵ or attempts at inducing/simulating illness. They may present to physicians or online in chat rooms on the internet.

Almost any condition can be simulated, e.g. phaeochromocytoma due to ingestion of vanilla extract. ICD-10 talks about the intentional production or feigning of symptoms or disabilities, either physical or psychological [factitious disorder] where there are no confirmed physical or mental disorder, there is

¹⁷⁴⁹ *Munchausen's syndrome* in Asher's sense, perhaps 10% of all factitious cases. (Reich & Gottfried, 1983)

¹⁷⁵⁰ The DSM-IV-TR statement that factitious disorder patients wish only to assume the sick role may be too simple. Such cases may have multiple, mixed, changeable or unknown motivations. They may have Axis I (e.g. drug abuse) or II (e.g. borderline personality disorder) diagnoses. They may also, at times, malingere.

¹⁷⁵¹ In one study of renal calculi, 3.5% of the stones were non-physiological! (Gault ea, 1988)

¹⁷⁵² E.g. MBP = intentional production or feigning of physical or psychological signs or symptoms in another person who is under another's care in order to indirectly assume sick role.

¹⁷⁵³ Test the urine for phenolphthalein.

¹⁷⁵⁴ Use of exogenous insulin results in low C-peptide levels; oral hypoglycaemic drug use may raise C-peptide levels (mimicking insulinoma) by stimulating beta islet cells; oral hypoglycaemic drugs lead to measurable glibenclamide (glyburide in US) in urine.

¹⁷⁵⁵ A patient may accept prescribed medication without telling his clinician that he has had an adverse reaction to it in the past.

repeated and consistent feigning of, there may be self-cutting or abrading to induce bleeding, the use of toxins to simulate internal disorders, many investigations and operations at numerous centres despite negative tests, a presumed disorder of illness behaviour and the sick role, and signs of severe personality and interpersonal abnormalities.

The differential diagnosis is broad but includes pathological lying in hypoglycaemia, GPI, Ganser's syndrome, Korsakoff's confabulation, intellectual disability, bizarre histories in schizophrenia, hospital addiction¹⁷⁵⁶, malingering¹⁷⁵⁷, the gaslight phenomenon¹⁷⁵⁸, drug abuse¹⁷⁵⁹, psychoses,¹⁷⁶⁰ and hysteria¹⁷⁶¹. Some cases are difficult to classify.¹⁷⁶²

Contrasting behaviours¹⁷⁶³

	Behaviour evident + admitted	Behaviour under voluntary control	Behaviour directed towards obvious goal
Factitious	No	Yes	No
DSH*	Usually	Yes	Sometimes
Hysteria	No	No	Yes
Malingering	No	Yes	Yes

*Deliberate self-harm

MBP/FDP (Meadow's syndrome; Meadow, 1977, 1984, 1993; O'Shea, 1987; McGuire & Feldman, 1989), was first described in 1977. The mother may be a nurse¹⁷⁶⁴ or work in an occupation involved with touching, e.g. manicurist. The parents give false histories or fabricate signs in the child. The child may die as a result of such interference.(Wood, 2004) Fabrication may include feigned psychiatric or behavioural problems.(Schreier, 2000) The pregnant perpetrator may deliberately infect the amniotic fluid.(Porter ea, 1994) There is an absence of aspects of illness when the mother absent is absent; otherwise mother is in constant attendance.

Review of 451 cases of MBP (Sheridan, 2003)

Typical victim 4 or less years old, M = F, 6% end fatally

Mean of almost 22 months pass between start of symptoms and making of diagnosis

Over 60% of siblings suffer similar illnesses as do the index case

One-quarter of victims known siblings are dead

¹⁷⁵⁶ Looking for food and shelter, staying put, feigning illness or its exacerbation in order to stay in hospital.

¹⁷⁵⁷ These cases avoid dangerous procedures, have definite goals such as getting out of a war zone – 'Malingering is behaviour and not a diagnosis'.(Bass & May, 2002)

¹⁷⁵⁸ Make another person appear sick so as to have him/her committed to mental hospital - seen in marriage, nursing home, etc.

¹⁷⁵⁹ Munchausen patients use drug needs as a ruse and will leave hospital after confrontation despite offer of drugs.

¹⁷⁶⁰ Some simulators of psychoses have become psychotic eventually.

¹⁷⁶¹ True conversion is rarely found in Munchausen's syndrome.

¹⁷⁶² Other conditions that must be considered include **SHAFT syndrome** (patients who manipulate plastic surgeons into performing surgery, described as sad, hostile, anxious, frustrating, and tenacious: Kasdan ea, 1998), **multiple amputation seekers** ("Mania operativa passiva" or "amputee identity disorder" – very rare as when someone seeks removal of a healthy limb or places a leg in front of an oncoming train), the **masquerade syndrome** (presentation of school refusal as abdominal pain, headache, etc) **dermatitis artefacta**, people who have their **appearance altered to resemble an animal** such as a tiger, **simulated patients** (models used in training), and **pseudopatients** (journalists posing as psychiatric patients who were admitted in the US after complaining that they heard sounds such as 'thud' and who behaved normally thereafter; 11 of 12 cases were diagnosed with schizophrenia, the remaining case was given the label of manic-depressive psychosis; patients were more likely than staff to realise that the journalists were imposters, probably because they observed them more: Rosenhan, 1973).

One patient demanded admission because of Munchausen syndrome but his abdominal scars were washed off by staff!(Gurwith & Langston, 1980) An adolescent contaminated his urine in order to have pathology he believed to be present detected by investigation.(Reich ea, 1977) The first case was probably a true factitious disorder, whilst the other case most likely developed from concerns dating to surgery for hypospadias in early childhood.

¹⁷⁶³ In real life such distinctions are very difficult to make. Indeed real patients often change from from somatisation to factitious and malingering over time.(Eisendrath & McNiel, 2002)

¹⁷⁶⁴ It is essential to avoid miscarriages of justice, e.g. the Dutch nurse Lucia de Berk was jailed for 7 murders in 2003 but had her conviction quashed in 2010.

Poor prognostic factors in MBP, according to Bass and Adshead, (2007) are where there is harm done to the child, the child is sexually/physically abused/developmentally delayed/injured/somatizing, sadism, previous child deaths, harm to animals, problems with the parent (denial/uncooperativeness, personality disorder¹⁷⁶⁵, somatisation, alcohol/substance abuse, personal history of unresolved child abuse) or parenting (disordered attachment, lacks empathy for child, selfish) or family (conflict/violence, including across generations), professional difficulties) under-resourced, ignorant, prejudiced), and socio-environmental (violent neighbourhood that offers no support, involvement in false allegation network).

Extended forms of MBP include cases of abuse of elders, the intellectually disabled, and pet animals.

Prolonged psychotherapy and behaviour modification may help some cases of adult factitious disorder.(O'Shea & McGennis, 1982) Open acknowledgement of vulnerability of therapy to manipulation is helpful. Developing a therapeutic alliance offers best chance of enacting real change.

Management of MBP may involve multidisciplinary meetings, careful observation, laboratory evidence, police notification, court, psychotherapy, supervision, removal, etc. A high level of awareness and communication with all persons involved facilitates early diagnosis. The Royal College of Paediatrics and Child Health in the UK suggest in 2009 that a single responsible paediatric consultant should be the clinical lead and take responsibility for all decisions about the health care of the child.¹⁷⁶⁶ Expert opinions on MBP cases received much (sometimes adverse) publicity in Britain.(Anonymous, 2004; Dyer, 2005, 2006)

Dermatitis artefacta

Cotterill(1992) wrote that the skin is 'an organ of communication and patients with artefact dermatitis are very poor communicators...the only way that they can signal the rest of the world that they are angry or miserable is by developing simulated skin disease'.

*Pseudoseizures*¹⁷⁶⁷

These can occur in people varying from malingerers to true conversion cases.

Some potential features of pseudoseizures

Mimicking dramatic forms of epilepsy, e.g. tonic-clonic (often with changing motor activity, including non-synchronous or prolonged thrashing activity, during the 'ictus' in pseudoseizures)

Start at an older age than do true seizures (22 v 12 years)

Longer episodes of status

Closed eyes, resistance to attempted eye opening by examiner, or eye deviation to the ground when patient is turned on her side (the patient may still turn her eyes to the ground when turned to the opposite side); if eyes are open, convergence of eyes when a mirror is held up to the face

Observed attempts to control patient's hand held over the subject's face by the clinician

Ability to remember events despite bilateral convulsive movements

Prolonged non-responsiveness with full recovery

'Attacks' when under observation, e.g. in front of healthcare staff at a clinic

Uncontrolled cases with no early childhood onset and normal brains

History of overdose or self-injury, or other unexplained neurological disorders and abdominal pains

Retained pupillary and gag reflexes, a negative Babinski test

Incontinence, tongue¹⁷⁶⁸ or other injuries, and cyanosis are poor at differentiating pseudoseizures from legitimate cases. There is no rise or only a modest increase in prolactin above baseline¹⁷⁶⁹. Prolactin may not rise during true epileptic status.(Fink, 2000) Neurone-specific enolase, a marker of neuronal damage, rises after status, peaking 24-48 hours later.(DeGiorgio ea, 1999) Pseudoseizure cases are nearly always female. Pseudoseizures should be differentiated from *psychogenic seizures* that are evoked (deliberately or

¹⁷⁶⁵ Ford (2008b, p. 415) makes the point that severely narcissistic mothers may view the maltreated child as an object rather than as a person with all that that entails.

¹⁷⁶⁶ www.repch.ac.uk.

¹⁷⁶⁷ AKA: dissociative seizures, functional seizures, non-epileptic attack disorder/seizures/events, psychogenic epilepsy, pseudo-epilepsy.

¹⁷⁶⁸ Epileptics usually bite the side of the tongue whereas people with pseudoseizures may bite the tip of the tongue, the cheek, or a lip. If the tongue is badly scarred, however, the cause is more likely to be true epilepsy.

¹⁷⁶⁹ Only 72% of seizures show a rise in prolactin; false-negatives can arise with non-generalised fits; prolactin can rise after non-epileptic seizures; neuroleptics and the contraceptive pill increase prolactin.

not) by specific mental activity, e.g. arithmetic. *Déjà vu* is most often due to anxiety, and it lacks the vividness and repetitiveness of a temporal lobe epilepsy aura.

A history of child sexual abuse is common cases with conversion non-epileptic seizures¹⁷⁷⁰.

Videotelemetry is the most important test: a normal EEG during and just after an apparently generalised seizure favours a diagnosis of pseudoseizure. An observer may record an attack on a mobile 'phone.

Malingering

'The doctor-patient relationship is understood sacredly as a fiduciary relationship, a relationship based on trust'. (Dyer & Miller, 2003, p. 1635)

'Compensable injuries are highly resistant to treatment'. (Clarke ea, 2007, p. 226)

'Malingering is not a medical diagnosis but it does exist as an unwelcome shadow at the periphery of our discipline'. (Spence, 2010)

Malingering, which is by no means rare, (Rogers & Shuman, 2000) involves the intentional production of symptoms with a goal (external incentive) that is obvious when environmental circumstances are known, e.g. to escape from any intolerable circumstance, to avoid combat, receive compensation (e.g. combat veterans: Gold & Frueh, 1999), collect insurance, evade prosecution, obtain drugs¹⁷⁷¹, or to influence an interpersonal relationship. Antisocial personality disorder is over-represented in this area, particularly so in prison. *Adaptive malingering* includes survival tactics during such life-threatening circumstances as hostage-taking or being a prisoner of war. *Malingering by proxy* (Cassar ea, 1996) refers to circumstances where illness is fabricated in another person (e.g. a child) in order to achieve some external incentive (e.g. monetary assistance benefit or as 'evidence' in litigation proceedings: see Stutts ea, 2003), as distinct from factitious disorder by proxy wherein the motivation is thought to be achievement of the sick role by proxy. Malingering may be suggested by medico-legal context (referral by legal advisor), discrepancies between subjective complaints and objective findings, non-compliance with elements of diagnostics or management, or evidence of dissociality. Even hallucinations may be malingered¹⁷⁷². Estimates of the prevalence of malingering on neuropsychological testing varies from 33-64%. (Rao & Swanson, 2003, p. 27) A person should score better on easier test items than on more difficult ones and one a person exceeds his/her level of ability subsequent answers should be correct or false by chance. This idea is utilised in the *Validity Indicator Profile* (Frederick, 1997), i.e. there will be a disparity between expected and actual performance curves.

Dysmorphophobia (body dysmorphic disorder [BDD])

This chronic disorder (Oshea, 2000b; Phillips ea, 2006) had a mean age of onset in one study of circa 17 years and a mean duration of 9 years. There is a preoccupation with some real or imagined minor bodily defect¹⁷⁷³ that the patient feels is conspicuous. There is no true phobia and most cases have an overvalued idea, albeit expressed vaguely. Some cases reach delusional proportions. Non-delusional cases appear under hypochondriacal disorder in ICD-10 and delusional cases are recorded as delusional disorder, somatic type in DSM-IV. Insight may change and so redefine the phenomena from obsessional preoccupation through overvalued idea to frank delusion. There is no disorder of perception. Whilst the patient may be defining himself through his appearance (Veale, 2007)¹⁷⁷⁴ compliments about appearance have no ameliorating effect. Most common areas of concern are the overall appearance, face, hair, nose, genitalia, legs, skin, and multiple areas. Picking at skin is common, sometimes with secondary infection or scar formation. Concerns tend to shift from one body part to another. Some cases repeatedly check their appearance in mirrors whilst others avoid mirrors and cover up supposed defects with wigs or cosmetics. BDD must be distinguished from normal adolescent concerns about appearance, schizophrenia, delusional disorder, depression, nihilistic delusions, OCD, and anorexia nervosa.¹⁷⁷⁵ Cerebral blood flow studies suggest that these patients may have increased thalamic perfusion bilaterally as well as increased blood

¹⁷⁷⁰ Espc. with deep penetration and closely related perpetrator.

¹⁷⁷¹ E.g. a person malingers a history of narcolepsy in order to obtain a prescription for stimulants

¹⁷⁷² E.g. 'I saw a crowd of swans in monochrome', 'As soon as I lifted the blind I saw green men on the lawn', or the person's thinking or actions are inconsistent with experiencing hallucinations.

¹⁷⁷³ Or smell according to Marks & Mataix-Cols. (2004, p. 25) Patients with olfactory reference syndrome may try to disguise the 'smell', e.g. with perfume, deodorants, changes of apparel, frequent baths.

¹⁷⁷⁴ Veale (2007) suggests that Freud's Wolf Man may have had dysmorphophobia (a later analyst, Brunswick, described preoccupation with the nose associated with mirror gazing and constant powdering).

¹⁷⁷⁵ Life however is complicated, e.g. this author has seen a patient with dysmorphophobia, schizoaffective disorder and anorexia nervosa!

flow through the right pallidum and putamen. Abnormal asymmetry of the caudate and increased total white matter was shown on MRI. (Rauch et al., 2003) There is evidence from fMRI of abnormal visual processing and frontostriatal systems in BDD (Feusner et al., 2010) when patients respond to faces of various spatial frequencies. Case reports of BDD associated with fronto-temporal inflammation or chronic abuse of ciproheptadine (5-HT antagonist) and exacerbation with tryptophan depletion are listed by Perugi and Frare. (2005, p. 206) BDD is not uncommon in cosmetic surgery and dermatology clinic populations. Surgical correction of alleged defects is generally ineffective for the underlying dysmorphophobia. The patient may transfer his preoccupation to another body part after surgery. Rare cases may operate on themselves if turned down for cosmetic surgery¹⁷⁷⁶. CBT may help some cases, although its specificity awaits demonstration. Mild cases (and those also on medication) appear to make up most of the CBT literature and long-term maintenance may be needed. (Perugi & Frare, 2005, pp. 213-4) Clomipramine and the SSRIs are often effective as long as they are taken and have rarely been combined for resistant cases. (Veale, 2007) Antipsychotics are often given for psychotic states, although there are reports of such cases responding to antidepressants (SSRIs or clomipramine) given alone (e.g. Phillips et al., 2002) and pimozide added to fluoxetine was not more effective than placebo added to fluoxetine in a placebo-controlled study. (Phillips, 2005) However, this does not mean that antipsychotic drugs have no role. (e.g. Filteau et al., 1992)

Muscle dysmorphia (Hitzeroth et al., 2001)

Type of BDD where the person is unreasonably dissatisfied with their musculature/frame

Much more common in males

Excess working out, preoccupied with diet, abuse of steroids

Common in amateur body builders

May have other body dysmorphic preoccupations

Trichotillomania

Trichotillomania¹⁷⁷⁷ consists of ‘compulsive’¹⁷⁷⁸ hair pulling, from any part of the body, as single hairs or tufts. (Mansueto et al., 2007a,b) Various patterns are described: transient, episodic, and continuous. The hair may be collected or swallowed. The hair follicles show a characteristic change known as trichomalacia¹⁷⁷⁹. Some cases, particularly children, may also pull hair from other people or from pet animals. Females predominate. It may be related to stress, or at least exacerbated by stress. It has been described in a variety of circumstances and in a number of different psychiatric disorders¹⁷⁸⁰ and I.Q. levels. It usually presents in adolescence, but sometimes in childhood. It is a difficult disorder to manage. Trichobezoar¹⁷⁸¹ is an uncommon complication. Attempts may be made to cover up bald areas (wigs, hairstyles, colouring pencils, etc). MRI suggests structural grey matter changes in circuits¹⁷⁸² involved in habit learning, cognition, and affect regulation. (Chamberlain et al., 2008) A variety of psychological and physical (e.g. chlorpromazine) treatments have been advocated. Clomipramine and (to a lesser extent) SSRIs (serotonergic) seem to be more efficacious than desipramine (adrenergic), as they also do in OCD and other ‘habitual behavioural disorders’ such as kleptomania. N-acetylcysteine¹⁷⁸³, an amino acid and glutamate modulator (perhaps increasing extracellular glutamate in the nucleus accumbens), was significantly more efficacious compared to placebo in an American study. (Grant et al., 2009)

¹⁷⁷⁶ DIY cases include those who glue their ears back or use a hot iron for facial wrinkles! The patient should be asked to draw himself before and after surgery. Even if the patient is satisfied with the operation it is unlikely to alter the underlying disorder.

¹⁷⁷⁷ Term introduced by Francois Hallopeau, a French dermatologist, 1889. Gk *trich* (hair), *tillo* (pulling) and *mania* (morbid).

¹⁷⁷⁸ In fact some people do it whilst relaxed and, e.g., watching TV. Trichotillomania Learning Center, Inc at 303 Potrero Street, Suite 51, Santa Cruz, CA 95060, USA (831-457-1004 or www.trich.org) is a useful resource.

¹⁷⁷⁹ Punch biopsy shows increased catagen hairs. The upper follicles and infundibulum show melanin casts and granules.

¹⁷⁸⁰ Comorbidity is common: mood and anxiety (including panic, GAD, and simple phobic) disorders, OCD (syndromal and sub-syndromal), eating disorders, and drug abuse. (Keuthen et al., 1998)

¹⁷⁸¹ **Trichobezoar** (hair ball) may lead to malabsorption, anaemia, peritonitis, pancreatitis, acute appendicitis, and perforation of small or large bowel.

¹⁷⁸² Increased density of grey matter in left striatum, left amygdalo-hippocampal formation, and multiple bilateral areas.

¹⁷⁸³ N-acetyl cysteine has also been used in schizophrenia. (Berk et al., 2008)

Behavioural approaches include habit reversal (use an incompatible competing response such as clenching fists when entering high risk situation), stimulus control (wearing gloves, hats, and so on to block pulling), and stress management (breathing control, deep muscle relaxation, or CBT). Outlook is better for young children than for adults. Some patients are so ashamed and in fear of ridicule that they withdraw from social interaction.

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14

Personality and its disorders

Brian O'Shea

'The few specialist services for patients with personality disorder operate mainly at the tertiary referral level, often in conditions of security'.(Coit, 2003)

'Greater public appreciation of the differences between behavioral disorders and pure "diseases" might help the public see the role of clinical treatment in a more appropriate light'.(Cohen, 2003, p. 70)

'Diagnostic criteria for [antisocial personality disorder] are little more than a catalogue of disruptive behaviours which, it has been suggested, merely medicalises "evil"'. (Mullen & Sullivan, 2007, p. 495)

Personality¹⁷⁸⁴

'The field of personology reflects the complexity of human nature'.(Akiskal & Akiskal, 2005, p. 495)

Maturity

Attributes:

Objective self-perception

Flexibility in face of change

Tendency to make own decisions/plans

Objective view of the world

Integration - aware of own attributes and determining psychological processes

Competence to express own abilities/needs without clashing significantly with prevailing culture

Cloninger (2002): individual differences in maturity defined by 3 characterological dimensions:

Self-directed e.g. responsible for own acts v blaming others

Co-operative e.g. reasonable v prejudiced

Self-transcendent e.g. insightful v superficial

Temperament

Emotional core of the personality – thought to be largely genetic – Kagan (1994) described two distinct temperaments (inhibited and uninhibited¹⁷⁸⁵) in infancy that describe the fearfulness associated with novel situations; another approach (e.g. Clark & Watson, 1999) opines three basic temperaments (positive or negative emotionality, and constraint¹⁷⁸⁶); Goldsmith et al (1987) listed four ways in which infants express temperament, i.e. activity with effects on the environment, reactivity to the effects of the environment, emotionality (e.g. intensity of emotion and time taken to calm down), and sociability (causing and responding to social interactions); Chess and Thomas (1986) wrote of ten infant temperament categories (activity level, rhythmicity of biological rhythms, approach-withdrawal, adaptability, threshold of responsiveness, intensity of emotional response, quality of emotional response, distractibility, ability to finish a task, attention span/persistence) from which three topographical characteristics are derived (easy, difficult, slow to adapt)

Character

Conceptual core of personality

¹⁷⁸⁴ Latin, *persona*, a mask – how others perceive us.

¹⁷⁸⁵ 15% of infants are *inhibited* (low spontaneity, quiet/vigilant, low social interactivity), 15% are *uninhibited* (interactive talkers), and at least half remain so into the second decade of life.

¹⁷⁸⁶ *Negative emotionality* (subservied by a behaviour inhibition system and noradrenaline) is associated with fear of a hostile universe whereas confidence characterises *positive emotionality* (subservied by a behaviour activation system and dopamine). *Constraint* (possibly subserved by serotonin) refers to the tendency to take the longterm view rather than simply reacting to emotions.

Character is less heritable and more easily influenced by society and culture than is temperament (Cools & Ellenbroek, 2002) – best seen as formed by environmental effects on temperament

Personality (various definitions)

‘Those characteristic patterns of behaviour *and* modes of thinking determining a person's adjustment to the environment’

‘Lifelong style¹⁷⁸⁷ of relating, coping, behaving, thinking, and feeling’

‘The relatively stable differences between people in those aspects of their emotional and interpersonal behaviour, motives and drives which determine their adjustment to social and other environmental situations’

Trait

Any persistent aspect of personality

Nomothetic perspective

Compares aspects of personality between individuals to discover group norms

Defines personality in terms of deviation from such *norms*

Idiographic perspective

Recognises rich complexity and uniqueness of the *individual*

Individual-centred

Non-specific

Personality disorder

Enduring behaviour patterns, of developmental origin, causing inflexible responses to many personal and social situations

Appears in childhood or adolescence and persist into adulthood

Not due to another disorder

Not to be diagnosed on a cross-sectional basis¹⁷⁸⁸

Personality change

Acquired

Secondary to brain insult, severe mental illness or extreme environmental deprivation

The inflexibility or rigidity of traits and their inappropriate exhibition foster ‘vicious circles that perpetuate and intensify already present difficulties’. (see Millon & Davis, 2000) As exceptions to the rule, passive-aggressive (negativistic) and borderline personality disorder patients do not have rigid coping styles – they are openly ambivalent and unable to find a direction for their behaviour; they vacillate all over the place. DSM-IV criteria for personality disorder are given in the table.

Certain assumptions are often made in life cycle studies. According to the epigenesis approach, development occurs in successive, clearly defined stages. Each stage follows the previous one, and each must be negotiated successfully in order for development to proceed smoothly. Should a stage not be resolved, all subsequent stages reflect that failure in the guise of physical, cognitive, emotional or social maladjustment. In crisis points theory, on the other hand, each stage is characterised by a crisis point that must be successfully negotiated. Crises require adaptation. Each stage has at least one crisis point that differs from those of other stages.

Many factors interact in a complex way to produce our eventual personality: genes, experiences, culture, parents, other people, the environment, etc. Many different theories have been put forward to explain personality development. Illness, disease or dysfunction does not arise *in vacuo* but in a person with a personality. The disorder may be within the personality itself, or the personality's reaction to illness may colour or modify presentation of a disorder. Other factors are also important in modifying the clinical appearance of illness, e.g. culture and drugs. The latter are prescribed by licensed professionals, the self, lay acquaintances, or illicitly. Genes have an important influence on personality¹⁷⁸⁹. Also, in the context of environmental adversity, genetics become more important in the causation of ‘externalising disorders’ such as antisocial behaviour and substance use. (Hicks et al., 2009)

¹⁷⁸⁷ In reality certain ‘personality disorders’ may come on early (e.g. cluster B) and abate early whereas others (clusters A and C) may have a somewhat later onset and be more persistent. The diagnosis is relatively unstable over time and many clinicians are either extremely reluctant to make it or view it as a working diagnosis. (See Tyrer, 2010)

¹⁷⁸⁸ Cross-sectional assessment only tells us about personality functioning around the time of assessment.

¹⁷⁸⁹ E.g. MZ twins separated from birth have similar personality profiles.

Harari and Jackson (2007, p. 269) are critical of the fact that a person's response to discrimination or disadvantage may attract a psychiatric diagnosis, including one of personality disorder. Learning problems and psychological difficulties are common in any population of epileptics. Medication, especially the barbiturates, contributed to the so-called 'epileptic personality'. The *Mental Health Act 1983* (England and Wales) defined 'psychopathic disorder' as a persistent of disorder of mind (regardless of IQ) resulting in abnormal aggressiveness or seriously irresponsible conduct.

DSM-IV criteria for personality disorder

- (a) Enduring pattern (EP) of inner experience and behaviour that deviates markedly from the expectations of the individual's culture and is manifested in at least 2 of the following areas:
 1. cognition – ways of perceiving/interpreting self/others/events
 2. affectivity – range/intensity/lability/appropriateness of emotional response
 3. interpersonal functioning
 4. impulse control (this does not include 'impulse control disorders not otherwise specified' like gambling – Q.V. infra)
 - (b) The EP is inflexible/pervasive across broad range of personal/social situations
 - (c) The EP leads to clinically significant distress/impairment in social/occupation/other important areas of functioning
 - (d) The pattern is stable/long duration and onset dates at least to adolescence/early adulthood
 - (e) The EP is not better accounted for by another mental disorder/drug of abuse or medication/general medical disorder such as head injury
-

Hippocratic theory, of historical interest, is based on the four temperaments (see box).

Hippocrates and temperament

<i>Temperament</i>	<i>Body humour</i>	<i>Characteristic</i>
Melancholic	Black bile	Pessimistic
Sanguine	Blood	Over-optimistic
Choleric	Yellow bile	Irritable
Phlegmatic	Phlegm	Apathetic

Trait theory is basically an attempt at taxonomy. Introversion-extraversion¹⁷⁹⁰, body build types, and so on, are all based on the assumption that we, as people, occupy some point along some line(s) which are called trait(s).¹⁷⁹¹

Trait

An enduring, distinguishing, or idiosyncratic feature of personality

Factor analysis

A statistical technique used to determine the minimum number of items that explain observed differences/similarities between individuals over many different tests

Problems include poor predictive powers in many instances and the rather simplistic practice of 'explaining' traits by inference from what tends to vary over time, i.e. from behaviour.¹⁷⁹²

In 1936 Kretschmer described three personality types: pyknic, athletic and leptosomatic. Sheldon produced a similar classification (endomorphism, etc) in 1940. In 1942 he rated personality on three dimensions: viscerotonia - relaxed, enjoys comfort; somatotonia - assertive, energetic; and cerebrotonia - very controlled, not inclined to overt action, expresses himself symbolically. These are all attempts at classifying people according to somatotype (body-build), a practice that had some grain of truth in extreme cases.

¹⁷⁹⁰ Depending on whether our basic orientation is directed inwardly toward the self or outwardly toward the world at large.

¹⁷⁹¹ E.g. passive-assertive, confident-shy, and anxious-calm.

¹⁷⁹² Baca-Garcia et al (2007) found that the temporal consistency of mental disorders was poor, better for schizophrenia than for specific personality disorders, best for in-patient diagnoses and least for out-patient diagnoses.

Eysenck's theory: The most important input is from genes. Genes determine differences in reaction between individuals to the same environmental situation. Personality traits select the situation – situations do not determine conduct. Family environment (read 'genetic') is more important than wider (environmental) influences (e.g. school). There are three main traits (*vide supra*): E, extraversion – (ambiversion) – introversion; N, neuroticism – stability; and P, psychoticism – ego control. Stress + vulnerability = illness. He is highly critical of modern psychiatric taxonomies, seeing that as politically compromised committee resolutions, and recommends the dimensional over the categorical approach to diagnosis.¹⁷⁹³

Cramer (1994) interprets Eysenck's 'neuroticism' as reflecting emotional instability and his 'psychoticism' as meaning a lack of caring. Green and Smith (2010, p. 279) interpret Eysenck's 'neuroticism' as reflecting high levels of anxiety and depression but not necessarily attracting a diagnosis within the neurotic spectrum; they suggest that 'psychoticism' refers to eccentricity or un-socialised rather than psychosis as such.

Robert Cloninger (Cloninger, 1987, 2002)

Dimensions preferable to categories (supported by Morey ea, 2007)

Temperament is the emotional (limbic, hypothalamic) and character is the higher cognitive (mental self-government; thalamocortical, frontal cortex) aspects of personality respectively

Four temperamental dimensions: harm avoidance (anxious v daring), novelty seeking (exploring/impulsive/irritable/aggressive v frugal/stoical), reward dependence (social sensitivity attachment v insensitive/alooof), and persistence (industrious/determined v underachiever)

Character traits include self-directedness (purposeful/resourceful v aimless/helpless), cooperativeness (helpful/principled v hostile/opportunistic), and self-transcendence (inventive/insightful v unimaginative/undiscerning)

People with personality disorders have immature characters and show low self-directedness and low-cooperativeness

Cools and Ellenbroek (2002) detect some correspondence between Cloninger's temperaments and the ancient Greek humors as well as with basic emotions (anger, fear, love, tenacity).

Five-Factor Model (Wiggins, 1997)

First used to describe 'normal' people

Applied later to describe personality disorder

Clinicians may find it more difficult to apply than the categories of DSM-IV (Rottman ea, 2009)

Five dimensions:

Neuroticism (unstable emotion, negative affect)

Extraversion (energy, sociable)

Agreeableness (non-confrontation, warm)

Conscientiousness (responsible, organised)

Openness (to new ideas, not rigidly traditional)

These dimensions are composed of lower order *facet traits*¹⁷⁹⁴, e.g. extraversion contains assertiveness, warmth, positive affect, and a wish to experience excitement (briefly, these are gregarious people)

Dimensional Assessment of Personality Pathology (Livesley ea, 1989):

Mainly concerned with lower level traits

Later simplified into four broad factors (neuroticism, disagreeableness, introversion, and compulsivity), so bringing it close to the Five-Factor Model (Livesley ea, 1998)

¹⁷⁹³ He draws parallels between the ancient Greek temperaments (melancholic, choleric, phlegmatic, and sanguine) and his dimensions (unstable v stable and introverted v extraverted) so that rigidity (twixt introverted and unstable: melancholic), reliability (twixt introverted and stable: phlegmatic), easy-going (between stable and extraverted: sanguine), and impulsive (between extraverted and unstable: choleric) can be neatly plotted on a diagram. It is possible that these insights owe more to the similar meanings of words from different languages than to any revelations about what makes people tick.

¹⁷⁹⁴ For Morey ea, (2007) five-factor facets did not improve on validity of higher-order factors upon cross-validation.

Categorical and dimensional schools in psychiatry are uneasy bedfellows, with, classically, psychiatrists generally belonging to the first camp and psychologists favouring dimensions. (Marcus et al., 2006) In truth, we do not know which is most valid and both approaches have a role to play: categories for describing clinical disorders and dimensions to structurally assess personality. (Ansell & Grilo, 2007, p. 635) Many psychiatrists view both the neuroses and the disorders of personality dimensionally as exaggerations of normal. Kendell et al. (2004, p. 255) prefer a dimensional approach for personality disorder. Likewise, Schneider (1950) decried categorisation because he felt that personality, which he believed was genetically endowed, was too rich and complex to be described so narrowly. He advocated a description of the personality rather than a label. Community studies tend to support a dimensional approach, personality disorder being on a continuum with 'normal' personality. (Livesley & Jang, 2000) Livesley (2005) does not accept that discrete categories of personality disorder exist: 'features of personality disorder merge with normal variation and with each other'.

Skodol and Bender (2009) discussed the possible approaches to describing personality disorders in DSM-V. They point out the deficiencies of categories: overlap, heterogeneity within categories, vague boundaries with 'normals', and the fact that the 'not otherwise specified' category is the most heavily populated! Clinicians are most familiar with categories. Approaches centred on variables measure how they describe an individual patient whereas those centred on the patient look for closeness of (dimensional) match between a prototype and the patient. Trait-based dimensional approaches include many continuous variables on which all of us vary.

Tyrer's (2007) personality diathesis model suggests that personality disorder carries a vulnerability to an Axis I disorder that may or may not be manifest. He points out that personality disorder does not disappear when an Axis I condition erupts. Vulnerability is more a dimensional than a categorical notion.

Freudian analytical theory recognised certain psychosexual stages in personality development with some variation in their timing.

Oral stage

First year of extrauterine life

Everything revolves about the mouth

Results of excesses of gratification or deprivation at this stage: optimism, pessimism, self-love, demanding nature, dependence, ingratiating, jealousy and envy

Anal stage

Centres round the anus and toilet training

Derived pathological traits: orderliness, obstinacy, stubbornness, frugality, parsimony, ambivalence, defiance, sadomasochism and rage

Anal defensiveness is classically found in obsessive/compulsive neurosis

Urethral stage

Non-Freudian transitional phase

Shame resulting from inappropriate urination causes ambition and competitiveness as compensatory devices

Phallic phase

Child is focused on his genitals

Masturbates and imagines having sexual relations (oedipal¹⁷⁹⁵)

Experiences anxieties

Resolution of **oedipal conflict** allows development of superego by identification with influential others and externalisation of drive impulses towards constructive ends

Latent stage

Sexual impulses are quiescent (this is controversial)

Child plays mainly with same-sexed partners and learns many living skills

Child may develop excessive or absent inner controls

Genital (adolescent) stage

Intensified libidinal drives

Old conflicts reopened and must be resolved to achieve mature sexual and adult identity

¹⁷⁹⁵Oedipus, a character in a play by Sophocles.

Adult psychosexual problems (Erikson's identity diffusion) may result from non-resolution of this phase

Abraham suggested that arrest at the oral, anal, and phallic phases respectively led to dependent, obsessive-compulsive, and hysterical character types. Later theorists have put greater emphasis on the shaping influences of extra-psychic factors, such as interpersonal relationships, and socio-cultural influences.

Main 'regulatory (defence?) mechanisms' (according to Millon and Davis, 1996) of personality disorders as they appeared in various versions of DSM

schizoid – intellectualisation

avoidant - fantasy

depressive – asceticism

dependent – introjection

histrionic – dissociation

narcissistic – rationalisation

antisocial - acting-out

sadistic – isolation

compulsive - reaction

formation

negativistic (passive

aggressive) – displacement

masochistic – exaggeration

schizotypal – undoing

borderline – regression

paranoid - projection

Object relations theory¹⁷⁹⁶ concerns the relation between subject and object (another person) as unconsciously perceived by the subject. Internal representations of people are not necessarily realistic. Personality is shaped by early relationships with parents. For example, parental deprivation causes dependency, struggles with parents leads to obsessive-compulsive traits, and parental eroticisation and competition contribute to hysterical traits.

Social learning theory looks at the behaviours that we acquire in our attempts at coping with life. The environment we live in and the situations we experience are emphasised. We learn by direct reinforcement (we like rewards) and by mimicry. (Bandura & Walters, 1963) We discriminate between behaviours depending on how they are received and responded to by others and by the environment. Cognition is more important in determining behaviour than are instincts. 'Basic trust' was described by Erickson: children who receive satisfactory parenting at an early age and who have not been exposed to traumatic separations, and who have learned gradually to cope with normal separations, enter adult with a sense of 'basic trust' and self-confidence. This results from being able to draw on a 'mental representation' or internal image of reliable parental figures¹⁷⁹⁷. Harlow demonstrated that monkeys separated at birth from their mothers become behaviourally disturbed, impaired sexually, poor socialisers, and rejecting of, and aggressive towards, any offspring that they may bear. Early learning occurs at a presymbolic level and cannot be recalled or unlearned. In most cases of personality disorder it is probably true that problem behaviours accrue gradually through repetitive learning experiences and, contrary to popular experiences, single experiences only account for a small percentage of cases.

In the case of borderline personality disorder it has been argued that it may arise from the lack of constants like customs and values in modern society. Adults then reflect the contradictory and changing customs and beliefs of contemporary society and are left without a feeling for a 'core' to their being: 'the great unrequited'.

Evolutionary necessity theory states that personality disorder depends on context, i.e. excessive aggression or timidity may be adaptive under certain (e.g. harsh) circumstances and at certain times and that great diversity may be necessary for the survival of the species. (e.g. Allman, 1994, Weiner, 1999)

Situationist theory stresses the importance of environment in behaviour determination, e.g. if one randomly assign students to a guard role or a prisoner role the former may quickly act brutally toward the latter, as shown by Hanley's experiments during the 1970s.

Phenomenologists stress how different people perceive and interpret events.

Humanists emphasise positive attributes. Everyone has a unique life experience and personality can only be understood from knowledge of that experience (idiographic). The American psychologist Abraham Maslow (1908-1970) believed that we strive to reach the highest level of personal functioning and he wrote about climbing a pyramid of personal integration. Carl Rogers (1902-1987), an American psychologist and clergyman's son, believed that we innately tended to move in the direction of growth, maturity and positive change. Personality was a reflection of self-image and interactions with other people and the environment. Reflecting back what has been said by the patient by the therapist allows recognition of alternative views of perceived problems. Important themes in the patient's experience are sought. The therapist's role involves providing unconditional positive regard for the client and reacting in a warm, empathic and genuine way. Giving of advice is not central. Rather the therapist helps the client to heal himself. Kohlberg (1980) has subdivided moral development into three levels. The pre-conventional level (up to 6-7 years) is one of self-interest and obedience aimed only at avoiding punishment or receiving a reward. The conventional level (starts at about 6 years) is characterised by an appreciation of the importance of conforming to rules,

¹⁷⁹⁶ While Ronald Fairbairn (1889-1964) coined the term 'object relations', Melanie Klein (1882-1960) is the person most associated with the 'theory'. Other pioneers included D W Winnicott (1896-1971) and Harry Guntrip (1901-1975).

¹⁷⁹⁷ John Bowlby (1907-90) observed the effects on British children being separated from parents and evacuated into the countryside to evade the Nazi blitz. He believed that insecure attachments formed early in childhood left a person vulnerable to develop psychopathology, even a disorder of personality. A child who is emotionally deprived or abused in some way may employ defences that are meant to fix or stabilise, but end up inducing dysfunction. Donald Winnicott (1896-1971) wrote of the *false self*: the child who has unempathic, traumatising parents has to accommodate to such an environment. Such traumatising may be multi-generational. The capacity to survive in the physical absence of the mother is developed by the 4-7-year-old by relying on the internalised caregiver, itself a product of *good enough* parenting. Heinz Kohut (1923-81) stated that healthy development flowed from internalising empathic parenting in order to be capable of self-soothing.

obligations, and a consideration of the views of others. This type of reasoning has been seen as important in adolescence and as the most common type of reasoning in adults. In the post-conventional level, said to be the highest form of moral reasoning, one understands the complexity (shades of grey) of values and rules and appreciated ethical principles.

'Self' concepts include the ideas, perceptions and values that typify 'I' and 'Me'. How one sees the 'Self' affects the way we perceive other things. We act in accord with our self-image and repress feelings that are not in keeping with this. The perceived distance between the self and the ideal self, if wide, causes anxiety. **Type A behaviour**¹⁷⁹⁸ is reminiscent of the executive, who is always on schedule, works extremely hard, is competitive and aggressive. It is said to be associated with coronary artery disease. An interesting phenomenon in psychiatry is seen when two men go on strike from work: the busy, enthusiastic worker becomes anxious or depressed whilst the lazy man relaxes. Similarly, the breaking of a leg means more to a national cycling champion than to a loafer. It may be that type A individuals are highly defended and that work allows them to avoid neurotic problems.

Genetics: Most measurable aspects of personality appear to be at least moderately heritable. The human 5-HT transporter (5-HTT – necessary for fine-tuning serotonin transmission) gene is encoded by a single gene (SLC6A4) on chromosome 17q12. A small percentage of inherited variance (7-9%) and of total variation (3-4%) in anxiety-related personality traits appears to be related to 5-HTT gene polymorphism. Proposed linkage between D4 dopamine receptor gene alleles and novelty-seeking has yielded mixed results. (Kluger ea, 2002)

Panic attacks in adolescence may be a marker for any personality disorder during young adulthood. (Goodwin ea, 2005)

A Norwegian multivariate twin study (Kendler ea, 2008) found that genetic risk factors for DSM-IV personality disorders were not supportive of the notion of clusters A, B, and C in the DSM. Instead, one genetic factor reflected broad vulnerability to personality disorder pathology and/or negative emotionality. The two other genetic factors more specifically reflected high impulsivity/low agreeableness and introversion. Interestingly, the DSM clusters was well reflected in the structure of environmental risk factors. In other words, the tendency to clustering may be due to environmental experiences.

Personality of psychiatrists: There is some evidence that the personality and social attitudes of psychiatrists may, at least in part, influence their choice of treatment modalities, e.g. conservatives may incline toward physical treatments with radicals opting for psychotherapy.

Locus of control¹⁷⁹⁹: People, on this basis, are divided into internals ('my own efforts count') who seem to cope well and externals (attributing everything to fate, luck, other people, etc.) who cope less well.

*Burnout*¹⁸⁰⁰

Burnout is a major problem in modern human services. Some occupations may be at greater risk than others, e.g. deliverers of health care. (Evans ea, 2006) Persistently elevated occupational stress, coupled with lack of peer support and idealistic rather than realistic expectations of self and others, may lead to demoralisation, emotional exhaustion, and cynicism.

Features of burnout

Loss of humour
 Persistent sense of failure
 Anger, irritability
 Marital conflict
 Clock watching
 Increasing resistance to go to work each day
 Reluctance to see patients
 Increased use of psychotropic drugs
 Sleep disorders
 Accident proneness
 Minor ailments

¹⁷⁹⁸ Described originally in 1974 by Friedman and Rosenman.

¹⁷⁹⁹ Rotter introduced this concept in 1966.

¹⁸⁰⁰ The term was coined by HJ Freudenberg in 1974.

Increasing thoughts of leaving work
 Rigid thinking
 Suspiciousness
 Dehumanisation of clients

Therapeutic interventions

'Detached concern' for clients
 Appreciation of small gains rather than demand for cures
 Adequate support peer support and sharing of work load and responsibilities
 Development of interests unrelated to work

Italian community mental health staff study (Lasalvia ea, 2009)

Almost 2 of 3 staff experienced severe job stress
 1 in 5 had burnout
 Highest risk of burnout in psychiatrists and social workers
 Lowest risk of burnout in support workers and psychologists
 Burnout predictors = high frequency of face-to-face interaction with users, longer time in mental healthcare, poor work group cohesion, and perceived unfairness

The most dedicated and enthusiastic are consistently found to be at risk. One instrument used by researchers is the *Maslach Burnout Inventory*.

Notes on personality tests¹⁸⁰¹

¹⁸⁰¹ Modern **tests of personality and behaviour** are often divided into *objective* (responses are objectively scored and interpreted according to normative data) and *projective* (asked to give meaning to unstructured test stimuli [e.g. pictures of people, incomplete sentences, and inkblots]), the theory being that the patient projects unconscious elements) groups. The most famous personality test is the MMPI-2 which was originally (1943) developed by a psychologist and a psychiatrist, Starke Hathaway and Charley McKinley, at the University of Minnesota. The MMPI-2 and MMPI-A (adolescents) are very Axis I oriented. The *Lubin checklist of psychopathology* looks for feeling tone - various adjectives are ticked off. Kane's *self-description questionnaire* or the HOQ (*hystero-obsessoid questionnaire*) have been used, for example, in anorexia nervosa and in overdosers; the latter failed to support the notion of hysterical traits in young female parasuicides. The HDHQ (*hostility and direction of hostility questionnaire*) has been employed with groups such as alcoholics to determine their extrapunitive-intrapunitive status. Questionnaires are best used with an intelligent group because the questions are often difficult to decipher. The *Firo-B* (Schultz) looks at characteristic ways of interacting with people, such as whether we move toward or away from them. Each of these tests is accompanied by manuals, which supply normal scores. The SSI (*symptom-sign inventory*) attempts to differentiate psychotic from neurotic and to tell the type of disorder present. The DPI (*dynamic personality inventory*) is analytically orientated and deals with Freud's developmental staging of personality development. Cattell's *16 PF* (personality factors) looks at traits (factor means trait). The *Personality Disorder Questionnaire Revised* is a self-report questionnaire. The *Millon Clinical Multiaxial Inventory - III* (MCMI-III) is a 175-item self-report questionnaire in true/false format. It searches for personality disorders and for Axis I disorders. The MCMI-III has much item overlap in the scales which poses problems in interpretation and the Inventory may best be viewed as measuring Millon's own views on personality rather than DSM-IV-TR diagnostic criteria. (Clarkin ea, 2008, p. 81) The *Personality Assessment Interview* has 344 items and a 4-point response format ('false' to 'very true') that are used to form 22 scales containing items that do not overlap. Included are 4, 11, 5, and 2 validity, clinical, treatment, and 2 interpersonal scales respectively. It can be scored by computer. The *Millon Adolescent Clinical Inventory* has a greater focus on Axis II disorders than has the MMPI. **Projective tests:** An ambiguous stimulus is presented which is open to the client's own interpretation. The person is all that he brings to mind at that moment. Examples of such tests are the *Rotter*, the *Bernventor incomplete sentences*, e.g. 'I want to know.....' (complete this), the TAT (*thematic apperception test* - Henry Murray, Harvard psychologist, developed this test in 1943 - look at a picture and tell a story about that has a start, a middle and an end and that describes how the people in it are thinking and feeling), and the CAT (*children's apperception test*). One looks at pictures and says what is happening now and what might occur in the future. The *Rorschach* (Hermann Rorschach, Swiss psychiatrist, published his test in 1921) consists of ten cards - the famous ink blots. What do you see in them? Marking this test can be quite complicated, e.g. Exner's Comprehensive system. (Exner, 2002) Other tests include the interpretation by the tester of drawings (e.g. a man, a tree, a house, etc), and *Blacky's pictograms* which were developed to see who would benefit from open versus closed prisons (e.g. if they put drawings inside given squares they were safe in open prisons). These tests, like all other tests, should never be interpreted in isolation from an appraisal of the whole case by the clinician. Eysenck (1994) believes that projective tests lack validity, that there are too many possible reasons for each choice of response, and that these tests attempt the impossible, i.e. they argue backwards.

Diagnosis of personality disorder is risky when based on hospital observation of an ill individual, although suspicions may be noted. Corroborative information should be sought from a reliable informant. The patient should be observed when clinically recovered from any 'Axis I' diagnosis. Personality tests may measure aspects that are of marginal or no clinical significance. Also, self-report instruments and interviews for personality disorders may show little agreement in terms of the patients they classify as disordered.

Examples of instruments used to diagnose personality disorders are *Structured Clinical Interview for DSM-IV Axis II Personality Disorders*¹⁸⁰², *Structured Interview for DSM-IV Personality Disorders* (Pfohl ea, 1997)¹⁸⁰³, and *International Personality Disorders Examination* (Loranger ea, 1994)¹⁸⁰⁴.

A longitudinal perspective is essential when diagnosing personality disorder. Cross-sectional observations offer the opportunity to develop hypotheses which can be tested in the firmament of time. How does the patient function in diverse life areas, such as with peers and authority figures, in affairs of the heart, or in occupational or educational settings? Are there recurrent themes, as when the patient meets with disappointment? Is he exploitative or callous?

Relationship with psychiatric illness

The relationship between specific personality disorders and specific psychiatric illnesses is not now held to be as strong as was previously believed. It is still recognised that having a personality disorder renders a person more vulnerable to developing a psychiatric illness. However, personality disorder may render a psychosis more difficult manage and schizophrenia appears to damage the personality (particularly if it develops early in life).

Epidemiology and definitions of personality disorder

According to various authors (Weissman, 1993; Samuels ea, 2002) the prevalence of personality disorder is 4.4 -18%¹⁸⁰⁵ of the general population (2-3%, mostly males, with antisocial personality disorder, and perhaps 2%, mostly females, with borderline personality disorder), the precise figure depending on the cut-off point used.

The WHO Mental Health Surveys (Huang ea, 2009) looked at DSM-IV personality disorders in 13 countries. Personality disorder was found more often in males and in the poorly educated. Cluster C disorders were more common in the previously married and the unemployed while young people were overrepresented in clusters A and B. Other results are shown in the following box. Personality disorders are highly comorbid with Axis I disorders but comorbidity does not account fully for the degree of impairment found in these subjects.

Estimated prevalences: DSM-IV Personality disorders in WHO Mental Health Surveys (Huang ea, 2009)

Any personality disorder – 6.1%
 Cluster A – 3.6%
 Cluster B – 1.5%
 Cluster C – 2.7%

There are many definitions of personality disorder. Schneider, in the 1950s, stressed personal or community suffering as a result of psychopathy (i.e. abnormal personality). Walton and Presly, in the 1970s, stated that personality is manifest in a person's social relationships, and can be regarded as consisting of what people actually do in social contexts. Personality disorder has been seen as an enduring pejorative judgement rather than a clinical diagnosis and there have been calls to abandon its use. To diagnose personality disorder the clinician is called upon to explore by clinical interview the person's pattern of relationships with other people including his behaviour with the interviewer himself. Personality disorders manifest

¹⁸⁰² SCID-II, a semi-structured clinical interview (119 sets of questions), assesses DSM-IV personality disorders as categories or dimensions. A screening version is available. Associated with Michael B First (who was Editor, Text and Criteria, for DSM-IV) and co-workers.

¹⁸⁰³ SIDP-IV, a semi-structured clinical interview (2 versions: 107 questions concerning specific disorders, and 101 questions in thematic version), assesses DSM-IV and ICD-10 personality disorders as categories or dimensions.

¹⁸⁰⁴ IPDE, a semi-structured clinical interview (99 sets of questions in ICD-10 version, 67 sets of questions in DSM-IV version) assesses personality disorders as categories or dimensions. A screening version is available.

¹⁸⁰⁵ Coid ea (2006) surveyed British households and used the Structured Clinical Interview for DSM-IV axis II disorders: weighted prevalence of personality disorder was 4.4%.

themselves across a broad range of situations, rather than in only one specific ‘triggering’ situation or in response to a particular stimulus - as with separation anxiety or morbid jealousy. In order to distinguish them from personality *changes*, ICD-10 described personality disorders as developmental conditions that appear in childhood or adolescence and persist in adulthood.

ICD-10 and personality disorders

Deeply ingrained and enduring patterns

Manifested as inflexible responses to a broad range of personal and social situations

Represent extreme/significant deviations from the way an average individual in a given culture perceives, thinks, feels, and particularly relates to others

These behaviour patterns tend to be stable and to encompass multiple domains of behaviour and psychological functioning

Often associated with various degrees of subjective distress and problems in social functioning and performance

Are not secondary to another mental disorder or brain disease, although they may precede or accompany other disorders

Not mutually exclusive and overlap in some of their characteristics

Divided in accord with trait clusters corresponding to the most frequent/conspicuous behavioural manifestations

Assessment should be based on as many sources of information as possible

The ICD-10, DSM-IV, and Tyrer and Johnson (1996) classifications are summarised in the box. DSM-IV divides personality disorders into three clusters: eccentric, dramatic, and anxious. The diagnosis is unlikely to be appropriate before 16-17 years of age. At least three of the traits or behaviours described in the clinical description in ICD-10 are needed for a diagnosis. The absence of narcissistic personality in ICD-10 was interpreted (tongue-in-cheek) by Millon & Davis (1996) as reflecting lifestyle differences between the US and Eurasia! In fact, as they acknowledge, some of the features of ICD-10 histrionic personality disorder suggest that the WHO may have sneaked narcissism in by the side door. Millon described 60 subtypes of personality disorder¹⁸⁰⁶. (Millon & Davis, 1996)

Personality disorder

(a) ICD-10 personality disorders (p.d.), F60-69

Paranoid p.d. – excessive sensitivity to setbacks/rebuffs, bears grudges, suspicious/misconstrues actions of others, excessive sense of personal rights, excessively suspicious of fidelity of spouse/partner, excessive sense of self-importance, and preoccupied with conspiratorial interpretations of events, personal and at large

Schizoid p.d. – gets pleasure from no/few activities, emotionally cold/distant, finds difficulty in expressing feelings towards other people, no reaction to praise/criticism, no need for a sexual relationship, prefers solitary activities, lives an introspective existence/dwells on fantasies, little or no close/confiding relationships and doesn’t desire them, and insensitive to social norms/conventions

Dissocial p.d. (syn. amoral, antisocial, psychopathic, sociopathic etc)– callous unconcern for feelings of others, irresponsible/no regard for social norms/rules/obligations, able to start but not maintain relationships, low frustration tolerance/easily becomes aggressive/violent, can’t experience guilt or learn from experience (especially punishment), and blaming of others/rationalisation/antisocial behaviour

Emotionally unstable p.d. – marked tendency to act impulsively, does not consider consequences, and affective instability; two variants: *impulsive type/explosive p.d.* (emotional instability, lack of impulse control, and outbursts of violence or threatening behaviour (especially if criticised), and *borderline type* (syn. borderline p.d., see below)

Histrionic (hysterical or psychoinfantile) p.d. – self-dramatisation, theatrical, exaggerates emotions, suggestible, shallow/labile affect, looking constantly for excitement/approval/attention, inappropriate seductiveness, over-concern with physical appearance

Anakastic (obsessional or obsessive-compulsive) p.d. – excess doubting/caution, preoccupation with detail, perfectionism that thwarts completion of tasks, excess conscientiousness/scruples, preoccupation with productivity to exclusion of pleasure and interpersonal relationships, pedantic, excess adherence to social convention, rigid, stubborn, wants others to do things his way, and unwelcome thoughts/impulses intrude into consciousness

Anxious (avoidant) p.d. – persistent tension/apprehension, poor self-image, preoccupied with being criticized/rejected socially (leads to avoidance), must be sure of acceptance before becoming involved, and restricts lifestyle to ensure physical safety

¹⁸⁰⁶ Reflecting the artificiality of the classification.

Dependent (asthenic, inadequate, passive, self-defeating) p.d. – leaves important decisions to others, undue compliance/subordination, unwilling to make reasonable demands, uncomfortable/helpless when alone – feels he cannot cope for himself, fears abandonment by close others and having to fend, and requires much advice/reassurance before making simple decisions

Other specific p.d. – eccentric, immature, narcissistic, passive-aggressive, etc
Unspecified p.d.

Mixed and other p.d. – mixtures of above or ‘troublesome personality changes’ due to co-existing affective or anxiety disorder

(b) DSM-IV p.d.

Paranoid – distrustful, suspicious, motives of others seen as malevolent

Schizoid – detached from people, limited range of emotional expression

Antisocial – disregards and violates rights of others

Borderline – unstable interpersonal relationships, self-image, and moods; impulsive

Schizotypal – social/interpersonal deficits (acute discomfort with, and reduced capacity for, close relationships), cognitive or perceptual distortions, eccentricities of behaviour

Narcissistic – grandiosity, need for admiration, and lack of empathy

Histrionic – attention seeking, excess emotionality

Avoidant – socially inhibited, inadequate, hypersensitive to negative evaluations

Dependent – submissive, clinging and needs to be cared for

Obsessive-compulsive – preoccupied with orderliness, perfection and control

Others, e.g. depressive/passive aggressive

(c) Tyrer and Johnson classification of personality (simplified)

Level	Classification	Description
0	No p.d.	Good capacity to form relationships; reasonable personal resources to help in adversity
1	Personality difficulty	Enduring behaviour patterns interfere with social function only if stressed
2	Simple p.d.	Particular & persistent abnormalities create major problems in many life areas
3	Diffuse p.d.	Fulfils criteria for a number of p.d.s (In fact most cases of p.d. fulfil criteria for multiple p.d.s – Millon & Davis, 1996; 3.5 diagnoses of p.d. per patient in Chisea & Fonagy, 2000; Tyrer (2008, p. 137) calls this phenomenon ‘the other multiple personality disorder’)

Reactions of professionals

These may take the form of hate, anger, avoidance, abandonment, over protectiveness, side taking¹⁸⁰⁷, anger against supervisors¹⁸⁰⁸, excess concern, over-investigation, etc. The management of staff splitting¹⁸⁰⁹ includes helping staff to ventilate and discussing how their feelings help to understand the patient. They should be helped to relax, to develop a sense of control, to be consistent, and to set limits for the patient without recourse to anger. (Fogel & Stoudemire, 2000) Personality disordered subjects utilise a disproportionate amount of mental health resources. There are no quick fixes for personality disorders (Silk, 2010) and clinicians should not confuse short- (e.g. relief of depression or substance detoxification) and long-term (personal maturation and survival) goals.

¹⁸⁰⁷ E.g. with patient against family or other staff.

¹⁸⁰⁸ Because feeling powerless or incompetent.

¹⁸⁰⁹ This may reflect psychic splitting on the patient’s part into ‘all good’ and ‘all bad’ staff.

*Individual disorders of personality*¹⁸¹⁰

'By their nature personality disorders cannot be cured but some individuals can be helped to make necessary changes so that their behaviour is less distressing to themselves or other people'. (Lloyd, 1991)

'Personality disorder may explain, but never excuse'. (Ferguson & Milton, 2000)

Antisocial personality disorder and the history of psychopathy

According to Derek Raymond in *The Hidden Files* of 1992, 'The psychopath is the furnace that gives no heat'. In psychopathological terms it is the polar opposite of obsessional personality disorder: superego agenesis v hypertrophy.

Some definitions of psychopathy

Alexander (1930): *psychoneurosis* (repressed impulses cause anxiety, depression, obsessive-compulsive and hysterical symptoms) and character neurosis (same repressed drives lead to apparently purposeless and self-defeating antisocial behaviour)

Scott¹⁸¹¹ (1960): no other cause for the behaviour can be found; starts at an early age; abnormal aggressiveness or inadequacy with serious antisocial or asocial tendencies; and society feels it necessary to intervene

Craft (1966): psychopath differs from ordinary criminal because antisocial acts are often self-defeating, motivation is obscure, and abnormal conduct extends into many interpersonal areas

The term psychopathy may refer to a zone between lunacy and normality or to 'antisocial personality disorder'. The term personality disorder in general and the narrower concept of psychopathy are intermingled historically. There is some overlap with the neuroses, although it has been said that most neurotics do not have a personality disorder. (Tyrer et al., 1983) Gunn, a forensic psychiatrist, gave a different opinion during the 1970s: psychopaths are neurotics who handle problems antisocially. He later warned that since everyone except psychiatrists thought psychopaths required help we might be turned into jailers by the authorities. (Gunn, 2000) In a study of the extent to which normal personality variation accounts for comorbidity of a number of common psychiatric and substance use disorders, Khan et al. (2005) found that, whilst novelty seeking was modestly contributory to comorbidity between externalising disorders, neuroticism seemed to be a broad vulnerability factor for comorbid psychiatric disorders. Porter, (2001, pp. 296-7) a social historian, believed that earlier psychiatrists painted themselves into a corner by labelling 'vice, sin and crime' as mental disorder. The real truth is that the boundary between psychiatry and public opinion is too transparent.

History

1801, Pinel: people with sanguine fury and blind tendency to violent acts but who knew they were doing wrong - non-confusional mania or *manie sans délire*

1812, Benjamin Rush: morally deranged individuals; aggressive, irresponsible, callous, and shameless from early youth; possibly born with these tendencies

¹⁸¹⁰ Personality disorder categories are rarely discrete, most patients fitting the descriptions of a number of them. Also, personality disorder comes in all degrees of severity. A rounded picture of a patient's personality can be got from interviews from the patient, informants who know the patient well, and from tests of personality such as the *Personality Disorder Examination*. Multiple sources are superior to single sources. However, the information given by each may not be identical. (Riso et al., 1994) A study of treatment of major depression showed that comorbid personality disorder predicted poor social functioning and residual symptoms of depression. (Shea et al., 1990)

¹⁸¹¹ a forensic psychiatrist

1835, Prichard¹⁸¹²: *moral insanity* - devoid of cognitive or floridly psychotic features but with perverted impulses, feelings, morality, inclinations, etc: 'morbid perversion of the feelings, affections, and active powers, without any illusion or erroneous conviction impressed upon the understanding'
Moral imbecility: combination of mental handicap and moral insanity
 Henry Maudsley, borrowing the Morelian concept of degeneracy,¹⁸¹³ believed that some temperaments, occasionally inherited, while not psychotic under normal situations of stress, might readily become mad as a result of intrapsychic or environmental strain; he wondered if doctors were responsible for dreaming up the concept of moral insanity unjustifiably (i.e. such people were criminals)
 1888, Julius Ludwig August Koch (1841-1908) of Württemberg: *psychopathic inferiority* fell short of mental disorder
 Emil Kraepelin failed to satisfactorily classify psychopathy
 Analysts indict early rejection as the root cause of psychopathy - Rutter and Giller (1983) found evidence that parental divorce/separation were strongly associated with delinquency, whereas parental death bore only a weak association, i.e. discord seems to be key (Luntz & Widom, 1994) - weak attachments with caregivers, as in institutions, have long been seen as leading to poor development of internal controls
 Schneider's *affectionless psychopath*: conceptually close to modern idea of psychopathy
 1939, D. K. Henderson: 3 types of psychopath - *aggressive, inadequate* (passive¹⁸¹⁴) and *creative* - creative psychopath¹⁸¹⁵ is individualistic, carves a way through life, suffers no obstruction, and may become driven leaders
 Donald Winnicott (1896-1971), a British psychoanalyst, wrote that antisocial proclivities were due to a child being able to attribute deprivation to external forces (self-attribution leads to depression) and thereafter annoying others in order to get them to fill a void
 Cleckley (1964) divided psychopathy into *primary* (cold, aggressive and never upset), *secondary* (suffers more, high tension levels, low self esteem, hidden guilt or regret), and a possible third (*secondary to psychoneurosis*) types
 Cloninger (2005, p. 126) - two groups of impulsive, antisocial personality psychopaths: *primary* (cold, callous, without remorse) and *secondary or neurotic* (DSM-IV borderline personality disorder and ICD-10 emotionally unstable personality disorder, the latter being divided into impulsive and borderline subtypes)
 Marcus ea, (2006) using taxometric analysis, looked at male offenders in state prisons or court-ordered to residential drug treatment, and concluded that antisocial personality disorder exists on a *continuum* (i.e. best measured dimensionally) and that its origins are *multifactorial*

Distinguishing between subtypes can be difficult in practice. The present author prefers to distinguish between *primary* (recognisable to friends and family) and *subcultural* (normal antisociality within a locality) types. In the DSM system, the division of delinquency into socialised and under-socialised aggression has lost unfortunately favour and has been replaced by onset in childhood or adolescence and scoring as mild, moderate or severe. It is important that the normal (and transient) risk-taking and group effects found in adolescence are not labelled as being pathological.

Dolan (1994) lists possible causes of psychopathy as cortical immaturity (excess theta waves¹⁸¹⁶), chronic under-arousal (low autonomic arousal¹⁸¹⁷ and low electrodermal orienting¹⁸¹⁸)(Scarpa & Raine, 2002) leading to sensation-seeking¹⁸¹⁹, psychosocial deprivation, brain dysfunction¹⁸²⁰, heredity¹⁸²¹, and impulsivity¹⁸²².

¹⁸¹² James Cowles Prichard (1786-1848), English Quaker.

¹⁸¹³ Mental handicap, psychoses, epilepsy and criminality.

¹⁸¹⁴ It was suggested at the time that he was describing neurosis.

¹⁸¹⁵ Henderson suggested Joan of Arc, Napoleon and Lawrence of Arabia as examples of creative cases.

¹⁸¹⁶ But 15% of people have abnormal EEGs yet are not psychopaths.

¹⁸¹⁷ Low resting heart rate correlates with later criminality.

¹⁸¹⁸ People with antisocial personality disorder show reduced skin conductance during a social stressor.

¹⁸¹⁹ Less capacity for anxiety.

¹⁸²⁰ Pseudo-psychopathic states follow head trauma or cerebral disease involving in some but not all cases the fronto-temporal areas; association with ADHD; possible limited dominant hemisphere resources for processing verbal information.

¹⁸²¹ Some evidence from twin and adoption studies.(Christianson, 1970; Crowe, 1974; Cadoret ea, 1995) There seems to be a complex input from genes and environment in antisocial behaviour.(Silberg ea, 2007)

¹⁸²² 5-HIAA and platelet MAO may act as markers; reduced catecholamine output in response to stress; low MAO A activity may interact with adverse childhood to produce conduct disorder.(Foley ea, 2004) Antisocial personality may involve problems with not

The term psychopath should probably be confined to a personality type (dissocial, sociopathic) and not to personality disorders as a whole as was variably the case in the past. For instance, the obsessional personality and the criminal psychopath are not natural bedfellows. Psychopathy is often used professionally in a pejorative fashion.¹⁸²³

Many psychopaths learn from experience to avoid punishment in borstals and prisons yet find it difficult to stop getting into trouble despite knowledge of the probable consequences. Children with psychopathic traits may have a reduced ability to avoid frustration and this may relate to abnormal ventromedial prefrontal cortical function.(Finger ea, 2008)

Posterior temporal slowing of the EEG was found to be common in the young psychopath, although this is probably simply a reflection of immaturity rather than pathology. MRI work suggests an 11% reduction in prefrontal gray matter¹⁸²⁴. This could account for low arousal, poor fear conditioning, lack of conscience, and decision-making deficits. The amygdala is important in aversive conditioning, instrumental learning, and in responding to emotionally laden facial expressions¹⁸²⁵. MRI studies have also reported reduced amygdaloid volume (+/- surface deformations: Yang ea, 2009) in people with high levels of psychopathy¹⁸²⁶. fMRI revealed reduced amygdala response in the higher scoring (on PCL-R) group during processing of words of negative valence.¹⁸²⁷ fMRI also showed that psychopaths failed to significantly activate the limbic-prefrontal circuit¹⁸²⁸ during fear conditioning,(Birbaumer ea, 2005) leading the authors to suggest that dissociation of emotional and cognitive processing may underlie lack of anticipation of aversive events in criminal psychopaths. Disruptive youths with callous-unemotional traits fail to activate the amygdala when processing fearful expressions.(Marsh ea, 2008) The corpus callosum may be abnormal in psychopathy.(Raine ea, 2003)

Some, but not all, cases of maternal deprivation (Gao ea, 2010) and early institutionalisation show psychopathic tendencies later on. Maternal nutritional deprivation during early pregnancy in wartime Holland has been associated with antisocial personality disorder in young adult offspring.(Neugebauer ea, 1999) Schulsinger, in a 1972 Danish adoption study, found an excess of psychopathy among biological relatives of psychopathic adoptees over that of adoptive relatives. Adoptive parents may show negative parenting when the parents of their children had antisocial proclivities, possibly reacting to some inherited trait in the children.(Thapar & O'Donovan, 2002) Some people, again a minority, with an XYY sex chromosome constitution, have been associated with criminality; they also tend to be tall. However, most experts believe that the association is spurious. Novelty seeking may be associated with the type 4 dopamine receptor (but this was not so in a meta-analysis: Kluger ea, 2002) and the type 1 cannabinoid receptor. According to Fu ea, (2002) who studied male twin pairs who served in Vietnam, shared risks between antisocial personality disorder, major depression and marijuana dependence may be explicable as stemming from the antisocial personality disorder. It does appear that parenting style can moderate the

doing something despite negative consequences, and this tendency is found in animals who have a dysfunctional septo-hippocampal system. The neuronal isoforms of nitric oxide synthase may be involved in modifying various behaviours, including aggression, and deficits in neuronal signalling via nitric oxide in moderating prefrontal circuitry may be important in the origin of impulsiveness.(Reif ea, 2009)

¹⁸²³ 'He's only a PD!' Barbara Wootton (Baroness Wootton of Abinger, 1897-1988), British sociologist and criminologist, has called it a circular diagnosis: mental illness is inferred from antisocial conduct, and this term is then used to explain why he acts the way he does.

¹⁸²⁴ Cortical thinning in inferior mesial frontal cortices.(Narayan ea, 2007) Others report left posterior cingulate and right dorsal anterior cingulate gray matter concentrations as potential endophenotypes for psychopathic traits, with heritability estimates of 46% and 37% respectively.(Rijsdijk ea, 2010)

¹⁸²⁵ Criminal psychopaths differ from controls on MRI patterns when responding to various facial emotional expressions.(Deeley ea, 2006)

¹⁸²⁶ *On Hare's Psychopathy Checklist – Revised: PCL-R*. The screening version contains interpersonal/affective (superficial, grandiose, manipulative, lacking remorse, no empathy, doesn't accept responsibility) and social deviance (impulsive, poor control of behaviour, lacking goals, irresponsible, antisocial as adolescent and adult) factors. **Psychopathy is a narrower concept than antisocial personality disorder, insofar as the former may not have broken overt rules or have been caught doing so.**(Hart ea, 1995) Employing the *Hare's Psychopathy Checklist-Youth Version (PCL-YY)* and adjusting for associated conduct problems Fowler ea (2009) found that in children with ADHD total psychopathy scores were associated with maternal smoking during pregnancy, emotional dysfunction (callous, lacking affect, etc) scores were associated with birth complications, and neither was associated with family adversity.

¹⁸²⁷ For a review see Blair.(2003)

¹⁸²⁸ Amygdala, orbitofrontal cortex, insula, and anterior cingulate.

genotype of offspring, e.g. parental negativity and low warmth predicting antisocial behaviour.(Feinberg ea, 2007)

Wood and Park (2002) compared the results of a neuropsychological test battery in DSM-IV antisocial personality patients and controls. The former had impairments on dorsolateral prefrontal cortical executive function tasks of planning ability and set shifting. They were also impaired in ventromedial prefrontal cortical function.¹⁸²⁹ Boys with pure conduct disorder differ from normal boys and boys with pure ADHD on fMRI during a task measuring inhibitory control, with reduced activation in bilateral temporal-parietal regions in the former group.(Rubia ea, 2008) An fMRI study by the same group (Rubia ea, 2009) of male (aged 9-16 years) pure ADHD, pure conduct disorder, and healthy subjects found a process-related prefrontal dysfunction in both disorders: attention-related dysfunction in ventrolateral prefrontal cortex in ADHD and reward-related dysfunction in orbitofrontal cortex in conduct disorder.

Antisocial personality disorder is nearly always preceded by conduct disorder (see box) in childhood.(Hill, 2003; Simonoff ea, 2004) One study (Robins, 1978) found that only 40% of antisocial children became antisocial adults, but it was rare to find an antisocial adult who hadn't been an antisocial child. A 40 year follow-up of conduct-disordered adolescents (Colman ea, 2009) found that they were likely to leave school without any qualifications and to experience many social and health problems that had adverse effects on them, their families, and society. Children who have early feeding, washing, or dressing problems, who cry loudly, who protest at novelty, and who have tantrums may later be over-represented among the ranks of psychopathy. The earlier the onset of conduct disorder in childhood and the more pervasive it is the more likely is antisocial personality disorder to be present in adulthood.(Zoccolillo ea, 1992) Inequality of income may bear a stronger relationship to antisocial behaviour than does absolute wealth. Also, environmental deprivation is more closely linked to antisocial behaviour than is social class. A reduced resting heart rate has often been reported in studies of conduct disorder: a combination of relative bradycardia, reduced skin conductance, lesser amygdala¹⁸³⁰ response to fearful faces, and increased EEG slow wave activity suggests autonomic hypoarousal – all suggesting a reduced ability to become anxious or afraid. An fMRI study of males aged 16-21 years (Passamonti ea, 2010) whilst viewing different facial expressions found that those with conduct disorder had reduced responses in areas associated with antisocial behaviour: there was increased amygdala response to neutral but not angry faces; conduct disorder emerging in childhood was associated with relatively reduced amygdala response to sad compared to neutral faces and to sadness compared to adolescent-onset cases and control subjects. Some findings suggest a dysregulation of the hypothalamico-pituitary-adrenal axis¹⁸³¹ in conduct disorder and antisocial personality disorder.

Conduct disorder

Not an entity in itself

Various forms of unacceptable behaviour

Different levels of severity

Prevalence: 1% - 10%

M > F, but females may be catching up¹⁸³²

Reading disorder in one-third

Family (e.g. unstable home with absent/alcoholic father), socioeconomic (classically poor), and environment important in majority of cases¹⁸³³, but some come from 'good' homes; the combination of antisocial personality disorder symptoms and depression in mothers strongly increased the risk for children's antisocial behaviour in Kim-Cohen ea (2005); a broad range of externalising psychopathology in late-adolescent offspring is associated with alcohol and illicit drug dependence in their parents (Marmorstein ea, 2009).

Comorbidity includes affective disorder (espc. bipolar disorder: Arrendondo & Butler, 1994; Spencer ea, 2001), substance abuse (some evidence of role for chromosome 9q34: Stallings ea, 2005), ADHD, intellectual disability, psychoses, brain impairment

¹⁸²⁹ Go/No Go tasks and visual memory tasks.

¹⁸³⁰ Right amygdala responsivity in an fMRI study of callous, unemotional, conduct disordered boys.(Jones ea, 2009)

¹⁸³¹ E.g. low morning plasma cortisol levels.

¹⁸³² Girls' antisocial behaviour may differ from that of boys, e.g. malicious rumours are more likely to emanate from females!

¹⁸³³ Rutter (1990) holds that a positive relationship with a parental figure (at any point up to adolescence) is important in preventing conduct disorder. Childhood adversity associated with maladaptive family functioning is a strong predictor of chronic functional impairment.(McLaughlin ea, 2010)

DSM-IV diagnoses ADHD plus conduct disorder as comorbidity; ICD-10 would label the combination as hyperkinetic conduct disorder

Early (childhood v adolescent) onset (M > F) is more often associated with violence, ADHD, history of oppositional defiant disorder¹⁸³⁴, and adult antisocial personality disorder

Most cases of oppositional defiant disorder do develop conduct disorder

Caspi et al (2002) theorised that conduct grew out of early physical abuse but only if the person had a polymorphism of the MAO-A gene conferring low levels of MAO-A; those with higher levels were better protected against developing conduct disorder (see also Prom-Wormley et al, 2009)

Heritability of conduct disorder may be weaker in girls with earlier menarche (Burt et al, 2006)

Conduct disorder should be distinguished from 'subcultural' cases who 'adapt' to neglect, disadvantage, and antisocial peer group¹⁸³⁵

Management should aim at environmental change, especially education of parents¹⁸³⁶ (Scott, 2008)

'Multisystemic' therapy, an expensive intervention, utilises available systems in the child's environment (school, friends, family, etc) and tries to maximise positive interactions and outcomes

Management of psychopaths includes longterm support, counselling, insight-orientation, limit setting, and a multidisciplinary therapeutic set-up. CBT did not improve outcomes for aggressive community-living antisocial adult males (N = 52) with antisocial personality disorder. (Davidson et al, 2009) Other interventions have included therapeutic communities where psychopaths exert some controlling influence over one another, penal disposal, and drugs such as clopenthixol to reduce aggression, benperidol¹⁸³⁷ to reduce libido, disulfiram to prevent alcohol intake, and methadone maintenance programmes to keep the patient from illicit drug-seeking.

The outlook tends towards improved social behaviour with time (Paris, 2002) but there remains the possibility of domestic violence thereafter. Problems, ranging from illness to early demise, may result from accidents, drug and alcohol abuse, fighting etc. HIV infection is more likely in drug abusers if the abuser has an antisocial personality disorder. Maturation of the EEG might be a good prognostic sign. Many, if not the majority, of psychiatrists, hold that there is no legitimate treatment for personality disorder in general and psychopathic personality disorder in general.

Pseudologia phantastica (pathological lying)¹⁸³⁸

- Stories told are distinguishable from other types of lying in a number of ways
- Not entirely improbable and often built upon a matrix of truth
- Stories are enduring, unlike confabulation
- Not told for personal profit
- Non-delusional (when confronted with the facts acknowledgement of falsehoods can be elicited)

Pseudologues have an equal sex distribution¹⁸³⁹

I.Q. varies

At least 40% may have evidence of CNS damage/dysfunction

¹⁸³⁴ **Oppositional defiant disorder** (ODD) usually starts before a child is eight years old and may affect 2-16% of children. There is persistent defiance toward authority (teachers and other adults) characterised by hostility, resentment, and argumentativeness. The syndrome is more common in young boys than young girls but it affects the sexes equally by adolescence. Symptoms are more often displayed in front of people familiar to the child and may not be revealed to the clinician. A diagnosis of conduct disorder (vandalism, cruelty, larceny, etc) trumps that of ODD. Perhaps 25% of preschool ODD cases progress to conduct disorder and about 30% of conduct-disordered adolescents progress to antisocial personality disorder. Early onset, aggression, poverty, and parental drug abuse favour the development of conduct disorder. Female adolescent conduct disorder may progress to antisocial personality disorder and somatoform disorder, depression and other 'internalizing' conditions.

¹⁸³⁵ **Conduct disorder** is often divided into those with onset in childhood (boys > girls, neuropsychological impairment, prolonged course, and high risk of adult antisocial personality disorder) and those commencing in adolescence (little sex difference, no neuropsychological problems, and low risk [10%] of adult antisocial personality disorder). Social problems, especially deviant peers, are significant factors in the genesis of adolescent-onset cases, i.e. they are close to what are sometimes known as 'sub-cultural psychopaths' and are less likely to be viewed as deviant within their own neighbourhood than is the case with childhood-onset conduct disorder. The author is aware of inner urban dwellers who had no moral qualms about stealing from 'outsiders' but who were outraged if one of their peers stole from a neighbour! This may be a product of 'outsiders' being seen as 'haves' and the subculture/neighbourhood as 'have not's'.

¹⁸³⁶ **Parent education:** promote play and organise child's day, improve relationship with child, reward desired behaviour and consequences for unwanted behaviour should be calmly delivered and consistent, and give clear directions/rules. (Scott, 2008)

¹⁸³⁷ Evidence of effect is lacking and EPSEs are likely.

¹⁸³⁸ Originally described by Delbruck in 1891.

¹⁸³⁹ The inclusion of peregrination (wandering about from place to place) artificially raises male numbers.

Structural MRI suggest that excess prefrontal white matter distinguishes pathological liars from normals and antisocials (Yang ea, 2007)
 Functional MRI (Fullam ea, 2009) showed enhanced activation of ventrolateral prefrontal cortex during a deception paradigm

Emotionally unstable personality disorder (ICD-10). Such people act on impulse without considering the consequences of their actions. There is affective instability, minimal planning and frequent angry outbursts, with violent and explosive behaviour. ICD-10 divides this group into:

(a) Impulsive type

Uncommonly seen in clinical practice, such people are emotionally unstable, lack impulse control, have outbursts of violence or threatening behaviour, and are particularly likely to 'blow' if criticised. Such cases tend to behave within normal limits for most of the time. They may use the fear they engender in others for exploitative purposes.

(b) Borderline type/personality disorder (BPD)

BPD¹⁸⁴⁰ does not 'border' on anything. BPD has been seen as being in danger of becoming synonymous with personality disorder in general.(Tyrer, 1999) American psychiatrists described these patients as being disruptive at interview, sarcastic, argumentative, angry, and uncooperative. Such patients blame others for their problems and are self-centred. Borderlines recall less parental care than do non-borderlines, especially from the mothers. They are lonely, lacking in emotional tone, anhedonic, and have a low stress tolerance. Depersonalisation and derealisation were commonly observed. They show a lack of discernment despite normal intelligence. Regression and transient psychosis often occur during psychotherapy – thoughtless attempts to 'probe the emotional depths' of these patients may exacerbate the situation.(Nemiah, 1999) Other features include alcohol and drug abuse, self-injury¹⁸⁴¹, parasuicide, masochism, labile mood, criminality, and binge eating. Comorbidity with somatisation disorder, panic, GAD, and major depression¹⁸⁴² is said to be common, but the link with depression has been described as weak and non-specific (Gunderson and Phillips, 1991) and the association with bipolar disorder I and II as 'modest'.(Gunderson ea, 2006) Criteria for BPD are an admixture of symptoms (state characteristics) and traits. This fact and complications¹⁸⁴³ may account for suggested relationships with schizophrenia and affective disorders.(see, e.g. Livesley, 2005; Clarkin, 2005) Stone (2005b) suggests that there is no relationship to schizophrenia and some connection to affective disorders, especially bipolar II disorder. Early-onset bipolar affective disorder may be a risk factor for BPD.(Goldberg & Garno, 2009) There may be 'brief psychotic episodes'¹⁸⁴⁴ that tend to be stress-related, reversible, transient, ego alien, and unsystematised.

Adult prevalence varies from 0.7% in Norway to 1.8% in the USA, with 70% of cases being female.(Lieb ea, 2004) However, it has been suggested that whilst clinical samples demonstrate a female excess the sex distribution may be closer to equality in community samples.(e.g. Torgersen ea, 2001) Perhaps females are more likely to look for or be referred for treatment. Patients may show some or all of the features defined in the box.

Features of borderline personality disorder¹⁸⁴⁵

¹⁸⁴⁰ The modern concept of BPD dates to Adolf Stern in 1938 ('borderline group of neuroses'), entered DSM III under the editorship of Robert Spitzer, and received its name from Gunderson and Singer in 1975.(Stone, 2005a) The term 'labile personality disorder' has been suggested by Millon.(Millon & Davis, 1996)

¹⁸⁴¹ Even though depression may deepen prior to an act of self-harm, suicidal behaviour may more accurately be predicted by unstable emotions.(Yen ea, 2004)

¹⁸⁴² Gelder ea (1996) suggest that GPs treat uncomplicated depression and refer depression 'complicated by abnormal personality traits or disorders' to psychiatrists.

¹⁸⁴³ As distinct from 'comorbidity'.

¹⁸⁴⁴ The present author's experience suggests that careful observation of the patient is required before diagnosing 'psychosis' in such cases. The term 'quasi-psychotic' is sometimes applied. Pope ea (1985) diagnosed 'factitious psychosis' in two of their cases, both of whom also had factitious neurological symptoms. The term factitious is problematic in such cases because it has been variably defined as 'subconscious' or 'simply seeking (inappropriate) medical care'. Psychosis in borderline personality disorder may be associated with drugs or mood disorder.(Zanarini ea, 1990)

¹⁸⁴⁵ Relationships are stormy and self-centred. Overcompensation for inferiority feelings is obvious. They cannot bear being alone. Davies (1987) defines this personality disorder thus: 'A diagnosis of borderline personality disorder may be made when a patient with longstanding difficulties in his relationships reports symptoms that though not clearly psychotic suggest disordered mental

Identity diffusion – no consistent sense of identity
 Projective identification – unconscious attempt to force others, including therapists, to act out a particular type of behaviour
 Splitting – sees others as all good or all bad, frequent shifts of allegiance; adept at getting some carers to take sides against other carers¹⁸⁴⁶
 Chronic feelings of emptiness, impulsive self-mutilation, brief psychotic episodes, manipulative self-harm, very demanding in interpersonal relationships
 Increased incidence of major depression
 Commonly give a history of CSA – evidence suggests that this does not cause BPD but is part of a general parental neglect syndrome (e.g. Zanarini ea, 1997; Fossati ea, 1999)
 There may be nothing specific about BPD that would separate it from personality disorders in general as regards being a trauma-associated spectrum disorder or PTSD variant,(Golier ea, 2003) although the PTSD-BPD relationship is still a subject of much research (e.g. Axelrod ea, 2005)
 Likely to meet DSM-IV criteria for other personality disorders, especially histrionic, dependent, antisocial, passive-aggressive, and schizotypal (Links ea, 1998)
 PET suggests that metabolism is abnormal in frontal areas (Goyer ea, 1994)
 fMRI suggests that specific frontolimbic neural substrates are associated with emotional and behavioural dyscontrol (Silbersweig ea, 2007)

According to Benjamin,(1996) a chaotic family, traumatic abandonment, a family that does not allow autonomy or the expression of happiness but encourages misery and dependence, or one that offers nurturance only if the individual is miserable, may breed BPD. Crandell ea (2003) noted intrusively insensitive interactions between mothers with BPD¹⁸⁴⁷ and two-month-old infants. Hobson ea (2009) found that mothers with BPD usually demonstrated disrupted affective communication with their infants during a separation-reunion episode and they tended to be frightened and disoriented.

Family studies suggest that BPD is not related to schizophrenia. Because of a finding of shortened REM latency in BPD it has been suggested that BPD might be due to an underlying affective disorder. A high frequency of EEG abnormalities has been reported, including non-focal spike or sharp wave activity, and, sometimes, posterior temporal spike-wave discharges. MRI has shown reduced hippocampal volumes in female (males not tested) BPD and as yet it is unclear if this reflects early traumatic experiences.

Orbitofrontal cortex dysfunction may contribute to some core features of BPD, especially impulsivity.(Berlin ea, 2005)

Distel ea (2008) examined data (mailed self-report on BPD features) from twin samples in three countries and calculated that 42% and 58% of variation were heritable and unique environmental in origin respectively.

ICD-10 states:

Patient's self-image, aims and internal preferences (including sexual) are often unclear or disturbed
 There are chronic feelings of emptiness
 There is a liability to develop intense and unstable relationships with repeated emotional crises and excessive efforts to avoid abandonment

functioning'. Lynch (2008) discussed Linehan's 'biosocial' theory in relation to borderlines: emotional vulnerability (high sensitivity and reactivity and slow return to baseline), environmental invalidation (being told that one is wrong – this is associated with autonomic hyperactivity as shown by the galvanic skin response) and problems with regulating emotions interact. The person is hyperresponsive to environmental cues/triggers that lead to emotional dysregulation (Fertuck ea [2009] found that borderlines have an enhanced sensitivity to the mental states of others.). Patients feel estranged because they have no one to call on when troubled. Therapists need a 'consultation team' to call on for support because patients may dysregulate the therapist. Borderlines are better than controls at assessing facial expressions for all emotions. Treatment aims to prevent the self-cutting response and replace it with problem-solving.

Spitzer ea (1979) gave the following diagnostic criteria for BPD: abnormal self-concept, intense and chaotic relationships, excessive anger, self-injury, underachievement, unstable mood, unhappy and unsatisfied, poor tolerance for being alone, and requiring long-term support.

¹⁸⁴⁶ There may be alternating idealisation and demonising of others. This leads to brief and rocky relationships. Finally, when separation threatens, psychic decompensation follows with increasing levels of harm to the self.

¹⁸⁴⁷ N = 8; normal controls = 12.

There is a series of suicidal threats or acts of self-harm.

Brief periods of inpatient care may be necessary from time to time. Outpatient care tends to extend over years. The whole gamut of psychotherapies has been advocated.(e.g. Stevenson ea, 2005) Drugs are also used although the risk of abuse is increased; some authors eschew treatment of ‘secondary’ problems like mood problems or ‘voices’, suggesting that they improve once control over impulsiveness and anger is achieved. There is some evidence that SSRIs may reduce suicidality and impulsiveness. There is some evidence that increasing age may ameliorate BPD. The suicide rate has been estimated at a low of 3% and as high as 10%. Comorbid depression is said to increase the suicide risk. In the present author’s experience, a patient may appear to be doing very well between psychotherapy sessions and suddenly kill themselves because of an event outside the therapist’s control, e.g. being jilted overnight. There is some evidence that dialectical behaviour therapy (DBT) may give positive results, especially in reducing self-mutilation. Improvement may occur with the passage of time¹⁸⁴⁸: in a 6-year follow-up study, Zanarini ea (2003) found that impulsive symptoms resolved the most quickly, cognitive and interpersonal symptoms had an intermediate outlook, and affective symptoms were the most persistent features of BPD.

McMain ea (2009) compared DBT with ‘general psychiatric management’ (psychodynamic informed therapy and APA guideline-derived symptom-targeted pharmacotherapy) in a single blind study and found them to equally efficacious. Meares (2005) also employs a psychodynamic approach for borderline patients. There are moments during treatment when sense of self is disrupted by traumatic memories. Therapist empathy with the patient and reflections help the patient to think about and gain understanding of what is happening within the self and between therapist/others and the self (*mentalisation* or *reflective function*). According to Bateman & Fonagy (2008, 2009) mentalisation therapy has long-term beneficial effects, although Choi-Kain and Gunderson (2008), who see mentalisation as excessively broad and multi-faceted, are sceptical.

Zanarini (2005a) has presented follow-up evidence suggesting that both symptomatic remission and attainment of good psychosocial functioning are common among even very disturbed cases, remarking that they ‘get well, as if they are growing up out of this disorder’. She also points out that optimism, humour, an ‘iron constitution’, and common sense are important attributes of the clinician who works with BPD cases.(Zanarini, 2005b) Gunderson ea (2006) found that a greater number of DSM-IV criteria for BPD and a history of childhood trauma predicted a poor outcome at two-year follow-up. Zanarini ea (2006) found a better prognosis at 6 years in younger cases, no history of child sexual abuse, no family history of drug abuse, no anxious cluster personality disorder, less neuroticism, and greater agreeableness.

The use of attachment theory research (insecure attachment) in family therapy in an attempt to prevent BPD is still at an early stage of development.(Byng-Hall, 2002)

NICE (2009)¹⁸⁴⁹ produced a set of guidelines for treatment and management of BPD patients. The guidelines emphasise access to services in spite of diagnoses or self-harm, ensuring active involvement by the patient in finding solutions and considering choices, options and consequences; developing a relationship that is optimistic and trusting and non-rejecting; careful management of changes in or ending of treatment, e.g. preparing patients for a change of service provider; and care in its various stages should be the responsibility of community mental health services. The guidelines suggest that medication should not be used specifically for BPD or its symptomatic or behavioural manifestations, including transient psychotic symptoms. Drugs may be used during a crisis if indicated with an eye to dependence and overdose potential. Twice weekly psychotherapy sessions are to be considered by therapists. Local services should develop specific teams to look after personality disordered patients. A crisis plan should be in place and consulted when needed: be calm and non-threatening, look at the event from the patient’s viewpoint, use open and empathic questions, validate the patient’s experiences (do not minimise their reasons), promote reflection on potential solutions, wait until you understand the problem fully before suggesting answers, consider alternatives to admission (e.g. home care), and offer appropriate follow-up at a mutually

¹⁸⁴⁸ In a 10-year follow-up study 88% of of 290 inpatients cases remitted; of these, 39.3% by the second year, another 22.3% by 4 years, an additional 21.9% by 6 years, 12.8% by 8 years, and a final 3.7% by the tenth year.(Zanarini ea, 2006)

¹⁸⁴⁹ National Institute for Clinical Excellence (NICE) in UK. Download at www.nice.org.uk/CG78. There are quick reference and the complete guidelines.

agreed time. Admission is only for situations carrying significant risk to self or others or where involuntary treatment is indicated. The aims and duration of admission should be discussed and agreed beforehand. A Cochrane systematic review and meta-analysis of RCTs (Lieb ea, 2010) found that while drug treatment, especially with mood stabilisers and second-generation antipsychotics, may be useful in treating some core symptoms of BPD and associated psychopathology, it doesn't have much effect on the overall severity of BPD; SSRIs do not yet have a strong evidence base; and the authors suggest that medication be used for targeted specific symptoms.

Schizoid personality disorder. This disorder is not as closely associated with schizophrenia as suggested by Kretschmer in 1936. However, what goes under this heading changed dramatically over the years, leading McKenna (2007, p. 445) to wonder if it had not become synonymous with Asperger's syndrome!

DSM-IV divided 'schizoid' patients into

Schizoid - cold, anhedonic, solitary, insensitive, robotic, and mechanical

Schizotypal (see below)

Avoidant - hypersensitive, socially withdrawn, yet craving acceptance, passively detached

Differential diagnosis includes avoidant and schizotypal personality disorders and Asperger's syndrome. Schizoid patients have an intrinsic defect in the capacity to form social relationships. They prefer isolative hobbies: philately, gadgetry, computers, and pure math. Because these people fail to manifest the overt instability or eccentricity of schizotypal patients they are relatively uncommon in clinical populations (O'Flynn ea, 2003, p. 81) and may be over-represented among the homeless. (Rouff, 2000)

Schizotypal¹⁸⁵⁰ (personality) disorder. This heterogeneous disorder¹⁸⁵¹ (Miller ea, 2002) seems to be more closely related to schizophrenia (as reflected in ICD-10)¹⁸⁵² than is schizoid personality disorder. DSM-IV schizotypy is characterised by odd behaviour, thinking, perception and speech, with unusual beliefs, and ideas of reference. Such people, who often view themselves as non-conforming and creative, may drift toward fringe groups that support their odd thinking and beliefs. Therapists should take a formal stance, avoiding forays into humour.

Schizotypal disorder

Anxious, uncomfortable and inept in company¹⁸⁵³

Find it difficult to form relationships

Lack friends/confidants¹⁸⁵⁴

See themselves as different/outsidere

Suspicious, ideas of reference

Odd beliefs, magical thinking¹⁸⁵⁵

Aware of a 'presence' that others would not experience

Hallucination-like experiences

Unusual way of speaking, digressive, vague, odd

Constricted affect

Eccentric¹⁸⁵⁶

¹⁸⁵⁰ It was once called 'borderline' (i.e. borderline schizophrenia), not to be confused with BPD.

¹⁸⁵¹ The present author agrees with McKenna (2007, p. 447) that 'the existing diagnostic criteria do not seem to capture what is being described very well'.

¹⁸⁵² Although isolated schizotypal symptoms are seldom precursors of impending onset of schizophrenia, the risk being greatest when a combination of symptoms or signs are present. (Miller ea, 2002)

¹⁸⁵³ Low-dose antipsychotic cover may be helpful when a patient cannot avoid others, as when starting work in an office or commencing an educational course.

¹⁸⁵⁴ Interestingly, prolonged early maternal separation in children whose mothers reported early angry emotional behaviour was found to correlate with increased schizotypal personality disorder symptoms. (Anglin ea, 2008)

¹⁸⁵⁵ E.g. they may believe in telepathy and clairvoyance.

¹⁸⁵⁶ Mannerisms; socially unconventional; odd attire; awkward in company; talk to self in public.

Schizotypal personality disorder appears to be found more often than by chance in females with fragile X syndrome.

Avoidant (anxious in ICD-10) personality disorder ('born worriers'). Such actively detached people have the capacity and desire to relate socially, but fearing humiliation and disapproval they distance themselves from others. They are shy, courteous, restrained, introverted, and timid. To complicate matters, this is what most psychoanalysts mean by 'schizoid'!

Differentiation (Millon & Davis, 2000)

Paranoid - believes he is the object of a conspiracy

Avoidant - sees himself as ridiculous (but may interpret routine questions as criticism)

Schizoid - derives little from interpersonal relationships

Avoidants - interpersonal relationships are punishing; prefers advance notice of what others expect

Avoidant cases may have been very submissive when growing up¹⁸⁵⁷, or they may have had a longterm physical illness. Separation anxiety disorder may have occurred in childhood. Therapists may be milked for constant reassurance, especially that he/she will not desert the patient. In fact, the patient may resist progress to avoid ending treatment. The therapist must not exploit or encourage submissiveness, or to reject a clingy client. There is a very high comorbidity rate between avoidant personality disorder and social phobia (Pigott & Lac, 2002) leading some authorities to suggest that they are synonymous. They may share a common genetic basis.(Reichborn ea, 2007) Persons with either disorder have similarly elevated familial risk for social phobia.(Tillfors ea, 2001) CBT may be beneficial.(Emmelkamp ea, 2006) Long term use of buspirone (withdrawn 2009) is acceptable in these patients.(Tyrrer ea, 1997)

Histrionic personality disorder ('social butterfly')

Uncommon¹⁸⁵⁸

Slightly more common in females

Egocentric and often unaware of true feelings

Theatricality, attention-seeking, dramatic reactions to events, tantrums, excitability, dependency, emotional shallowness and lability, empty seductiveness, and suggestibility

Relationships rapidly formed and poorly sustained

Borderline personality traits are common (Stone, 2005b)

Males may abuse substances

Women may complain of physical symptoms with no cause found (Coid, 2003)

Narcissistic¹⁸⁵⁹ personality disorder

More common in males

Commonly encountered in forensic circles (Coid, 2003)

May be mistaken for hypomania

Not every narcissistic adolescent develops it

Explanations of its origins have varied depending on sex of patient

Female develops superficial sexuality because of perceived paternal expectations (father saw her as a beautiful doll)

Male responded to doting mother

Alternatively

- *primary group* - bred to believe they were superior to others

¹⁸⁵⁷ Psychoanalysts have suggested that avoidant people are fixed at a developmental stage where it 'was' acceptable to be very shy and fear strangers. Many people are shy right up into adolescence and it may be erroneous to regard them as having avoidant personality disorder.

¹⁸⁵⁸ Cultures differ in what is considered to be histrionic. There is considerable overlap between 'personality disorders' in real life, e.g. borderline and histrionic.

¹⁸⁵⁹ Ovid's (Publius Ovidius Naso, 43 BC-17 AD) poem has **Narcissus** in love with his reflection and then killing himself when he realises that this reflection is an illusion and not a true person. The term 'narcissism' was introduced by the English sexologist Henry Havelock Ellis (1859-1939) in 1898. Freud used the term to mean love of self or self-absorption. Psychoanalysts then used the term to describe a reaction to damaged self-esteem: 'narcissistic injury'. The term was applied to a personality type during the 1980s.

- *compensating group* - told they were failures
- *combined group* - told that they were both

Some cases do not conform to the classical arrogant picture but are, instead, outwardly humble and self-sacrificing but inwardly harbour a belief that they are better than others

Heinz Kohut (1913-1981) viewed the road to narcissism as developing via a grandiose-exhibitionistic self or mirror transference and an idealised parental imago (the object's representation out of conscious awareness) or idealising transference

Dependent personality disorder (DPD; 'passive-dependent' in DSM-I). Whilst there is little support linking orality, as suggested by Abraham, and DPD, parenting styles (e.g. discouragement of independence) may influence development of this disorder. These patients are submissive and appeasing in relationships and inhibit negative responses for fear of destroying a relationship. Whilst DPD patients may present with problems secondary to real or threatened loss of a relationship upon which the person depended, there does not seem to be a direct relationship between this personality disorder and adult separation anxiety disorder. (Manicavasagar ea, 1997) A psychiatrist with such tendencies may unconsciously seek nurturance and excessive gratitude from his patient, with predictable results! Transient dependence secondary to axis I or medical disorders do not qualify for a diagnosis of DPD. Group therapy may encourage efforts at autonomy by practicing alternative coping styles in a safe setting. CBT may help through promoting assertiveness. Role-playing techniques may also be beneficial. Families must be won over so that any changes in the patient are not met with negative responses. Depression may follow failure of clingy or autonomous behaviour.

Paranoid personality disorder (PPD). One theory is that people with this personality disorder were the victims of excessive rage and humiliation in childhood. Interestingly, the incidence of PPD in the offspring of parents with schizophrenia was not increased in a study conducted by Hans ea (2004) unlike the incidence of schizotypal personality disorder and, intriguingly, avoidant personality disorder. The incidence of PPD in first-degree relatives of patients with delusional disorder is increased. PPD may be more closely linked to this disorder than to schizophrenia.

Paranoid personality disorder

Self-important

Suspicious, mistrustful, sensitive¹⁸⁶⁰

Resentful, bears grudges

Jealous

Obsessive-compulsive (anankastic in ICD-10) personality disorder. Freud, in 1913, distinguished between what is now called OCD (a neurosis) and obsessive-compulsive personality disorder (OCPD). In OCD there were the symptoms of a breakdown in a person's efforts to repress impulses and thoughts. In OCPD, the antithesis of antisocial personality disorder, one had a character style reflecting successful repressions with supplementary reaction formations and sublimations. OCD patients are distressed by their symptoms (ego dystonic) and while OCPD patients may be worriers they view their symptoms as being adaptive (ego syntonic). Millon & Davis (2000) described thinking in OCPD as a 'paralysis of analysis'! Self-righteousness and a polarised view of the world are typical. There is an unwillingness to accommodate the views and methods of other people. In therapy OCPD patients talk so much that it is difficult to interject. However, once interrupted they may view the therapist as unhelpful or unprofessional. The association between OCPD and depression is sometimes said to no longer be as strong as it once was held to be, although this is open to dispute (Costa ea, 2005, p. 418) and there is some evidence for a connection with bipolar disorder (Rossi ea, 2001). Also, the present author is struck by how many 'house proud' depressives he has encountered. It is often stated that OCPD does not seem to increase the likelihood of developing OCD and that most OCD patients do not have OCPD, but, perhaps due to 'differences in conceptualization and diagnostic criteria' (Costa ea, 2005, p. 416) and associated 'shame and secrecy', (Rothenberg, 2005) the literature is somewhat contradictory on these points (Black & Noyes,

¹⁸⁶⁰ This makes treatment and research difficult as PPD patients suspect hidden motives. An essential first step is to develop a (tentative and often brittle) trusting relationship.

1997; Samuels et al., 2000; Gabbard, 2005). The OCP style is not so devoted to his labours that he neglects his dependants, whereas the OCPD may do so; OCPD patients make difficult co-workers but they may be successful in some roles. According to Costa et al., (2005, p. 416) the most frequently comorbid personality disorders associated with OCPD are avoidant, dependent, and passive-aggressive. OCPD is commonly associated with eating disorders. (Costa et al., 2005, p. 417) OCPD is also reported to be associated with paranoid personality disorder. (Stuart et al., 1998) Treatment is often avoided, unless pressure is exerted by third parties. (Gabbard, 2005) CBT may be helpful. When psychoanalytic psychotherapy is undertaken it is important for the therapist to take an active stance and to promote a focus on (avoided) feelings and the patient's need for control rather than engage in endless intellectualisation.

Passive-aggressive (negativistic in DSM-IV-TR) personality disorder

Included in the DSM as subject for research

'Passively' resists carrying out tasks

Sullen, argumentative, unfairly critical of authority, resentful of successful others

Complaining of how unfortunate and unappreciated they perceive themselves to be

When confronted they may exhibit contrition, only to become hostile and defiant shortly thereafter

It has been suggested that such people were spoiled early on but, for various reasons, are dethroned (say by a new sibling) and treated harshly

Lay term passive-aggressive refers to sabotage in the workplace

Depressive personality disorder. Another DSM subject for research, this category is characterised by gloom and doom, low self-worth (and often a negative view of others as well), brooding, worrying, pessimism, guilt, and remorse. It may overlap aetiologically with major depressive disorder but a twin study suggests that it is a distinct entity. (Ørstavik et al., 2007) However, some practitioners consider that depressive personality disorder is synonymous with dysthymia.

Personality change

ICD-10 bases this condition on the cause or antecedent of such change. Residual schizophrenia (F20.5) is excluded. F62 is called 'enduring personality changes, *not attributable to brain damage and disease*'.

There should not have been a previous personality disorder that explains current traits. The change is aetiologically traceable to a profound, existentially extreme experience. F62.0-9 includes enduring personality change after catastrophic experience/psychiatric illness/other/and unspecified. Examples include enduring personality change following torture or concentration camp experiences.

In practice, enduring personality change may follow trauma to or organic disease of the brain¹⁸⁶¹, severe mental disorders (particularly schizophrenia), and extreme stress such as hostage taking, concentration camp experiences, or torture. PTSD may coexist.

Enduring personality change due to catastrophic experience (ICD-10)

No prior personality disorder that explains current profile

Duration of 2 years or more

Permanently feels distrustful of a world that is viewed as hostile

Always feels changed/different

Constantly feels empty/hopeless

Feels threatened/on edge all of the time with no exogenous cause

Prognosis

With a general increase in longevity more people with personality disorders may reach old age than heretofore. (Mordekar & Spence, 2008) Age has various effects on personality. We often hear of the elderly that 'he became more like himself', i.e. an exaggeration of personality traits as age advanced. According to Pankratz and Kofoed (1988), 'Abstract judgement becomes more difficult with age... This phenomenon, known as hardening of the categories, results in overgeneralization and inflexibility'. Behaviours that lead to a diagnosis of personality disorder in youth may change expression so as to no longer meet the necessary

¹⁸⁶¹ 'Personality change due to a general medical condition' as found in DSM-IV, Axis I.

criteria for such a label, so-called 'heterotypical continuity'. Rosowsky and Gurian (1991) provide the example of prescribed medication misuse replacing earlier self-mutilation in borderlines. Also, what is maladaptive in youth may prove adaptive in old age, e.g. excess dependency may help one to accept nursing home care.

Stone (1993) reviewed long-term prognosis in the personality disordered. 10-25 year follow up of BPD showed a wide range of outcomes, from clinical recovery in at least half the cases to suicide in 3-9%. Certain factors, like artistic talent, were conducive to a better outcome, while others, such as parental cruelty, were associated with a poorer outlook. Prominent psychopathic traits are a bad sign in antisocials. Schizoids and schizotypals remain isolated and marginalised. Lenzenweger et al (2004) also found considerable variability in features of personality disorder over time.

Some forensic issues

'It seems clear ...that it is impossible at present to decide whether personality disorders are mental disorders or not, and that this will remain so until there is an agreed definition of mental disorder'. (Kendell, 2002)

A prison survey in England and Wales (Singleton et al, 1998) found antisocial personality disorder in 63% of remanded males, 49% of sentenced males, and 31% of females in both groups. The controversy surrounding the best approach to psychopathy continues. (Casey & Craven, 1999; Eastman, 1999) Most murderers do not have 'severe' mental illnesses or contact with mental health services. The commonest diagnoses among convicted murderers in this part of the world are personality disorder, alcohol misuse, and drug abuse. However, without assertive follow up, mentally ill ex-prisoners are prone to lose contact with services, to re-offend and end up back in custody.

Children of criminals or psychopaths adopted by 'normals' are more likely to show antisocial behaviour than the offspring of 'normals'. (e.g. Crowe, 1974)

The stealing of young children is a rare offence. Much data comes from prison cases. Most such children are quickly recovered since there may be no attempt to conceal them. They are usually well cared for. Personality disorder (ill defined with overlap of categories) or psychosis (usually schizophrenia) are common in perpetrators. The act may satisfy an emotional need, may be used to manipulate the environment, or may be impulsive and psychotic. It may arise from a custody dispute. A man may abduct a child for sexual purposes. Baby stealing has been described in association with pseudocyesis. (D'Orban, 1982)

In a series of women who killed their children, D'Orban (1979) found that 84% had some disorder, the commonest being a disorder of personality; 16% were psychotic.

In one study the great majority of those who assaulted their wives had a personality disorder. (Hart et al, 1993)

Firesetting (arson) in young people is often associated with conduct disorder, social deprivation, failure at school and family disharmony. Most cases are boys.

If the sole goal is to become sexually aroused, then sadism¹⁸⁶² should be placed among the paraphilias. It was in DSM-III-R as a proposed personality disorder requiring further study, but it was dropped for DSM-IV. Masochistic personality disorder was not in DSM-III, was sneaked into an appendix of DSM-III-R as 'self-defeating personality'¹⁸⁶³, was dropped for DSM-IV, and isn't in ICD-10. Objections included unfairness to the female sex (who may be victimised in relationships and end up with a label¹⁸⁶⁴) and possible confusion with depression. It has been suggested that people with masochistic personality disorder become hypochondriacal manipulators when they cannot obtain love and nurturance by other routes: an abusive attachment is better than no attachment. (Berliner, 1958) Freud, in the 1920s, distinguished 'moral masochism' (a guilty sadist wishes to suffer) from 'erotogenic masochism' (sexual perversion). His thinking from viewing masochism as part of a spectrum shared with sadism to one of Thanatos (the masochist wished for self-destruction).

¹⁸⁶² Kraft-Ebing introduced the terms sadism and masochism in 1882. Cesare Borgia is sometimes cited as a classic example of the sadist. In contrast to Freud, Horney, in the 1940s, believed that sadism wasn't necessarily sexual in origin - that is that personality-based attitudes were bound to manifest themselves at some stage through sexual activity. She felt that the central feature was a deep need to triumph vindictively.

¹⁸⁶³ What personality disorder isn't?

¹⁸⁶⁴ The objection is that the label implies that women 'were asking for it', i.e. the abuse!

Management principles

One can only help people to function better. They cannot be changed into a different person. Progress, if any, will be slow. Be clear about the aims of treatment. The aim should be change real life behaviour rather than simply look for change in the treatment setting. Anything treatable, such as depression, should be treated. Use techniques to modify the environment. It may be better to see patients briefly and relatively infrequently. Although rotation systems make it difficult, as far as possible the one therapist should continue to see the patient. A wide variety of approaches have been used, e.g. group and individual psychotherapies¹⁸⁶⁵, behavioural treatments (social skills training, CBT), and various drugs (antipsychotics, lithium, antidepressants, anticonvulsants, antiandrogens, disulfiram etc). Millon and Davis (2000) consider the psychotherapies just as good and just as bad as one another when applied to the personality disorders. Efficacy should be subject to ongoing scrutiny and spurious 'cures' should be studied critically. Treatment needs to be individually tailored. Development of a therapeutic alliance and acknowledgement of vulnerability to manipulation by therapists are important ingredients of any therapeutic approach. Overdose of drugs is common. The evidence-base for many drug-based 'treatments' for personality disorder is flimsy.

The *Dangerous People with Severe Personality Disorder Bill* was introduced in 2000 by the British Labour government with the aim of removing people who might commit future crimes from society. Dangerous and severe personality disorder (DSPD) involved increased risk of a personal with a significant personality disorder (and *because* of personality disorder) offending against others within 5 years leading to serious physical or psychological harm. The RCPsych came out against this, pointing out the difficulties involved in accurate prognostication. Anyway, 6 people would have to be detained to prevent 1 person acting violently. Certain prisons and special hospitals are assigned the role of detaining such individuals.

Pathological gambling

'Impulse control disorders not elsewhere classified' (DSM-IV-TR) are defined as failure to resist a drive to perform an act that is harmful to the practitioner or others, with or without conscious resistance or planning. The disorders involved are intermittent explosive disorder¹⁸⁶⁶ (aggression, assault), kleptomania (stealing¹⁸⁶⁷), pathological (compulsive) gambling (PG), pyromania¹⁸⁶⁸ (pathological fire-setting), and trichotillomania (hair-pulling). ICD-10 is very similar on this subject, using the umbrella term 'habit and impulse disorders' (F63). There is likely to be a genetic element in abnormal gambling in both sexes. (Slutske et al, 2010)

Tension or arousal increases before the event. There is a feeling of pleasure, gratification, or release at the time of the act, and the act is consonant with the immediate conscious wish of the person, i.e. it is ego-syntonic. Following the act there may or may not be feelings of regret, self-reproach, or guilt. The prevalence of PG in Britain has been estimated as 2-40/1,000 of the population. About 68% of the US adult population have gambled legally during the past year. (Lynch et al, 2004) It is more common in men,

¹⁸⁶⁵ *Mentalisation* (Bateman & Fonagy, 2004; Meares, 2005) tries to assist people to understand their reactions to others and the reactions of other people to their behaviour. Beliefs, feelings and desires are examined for this purpose. *Nidotherapy* (changing the person's environment rather than trying to change the person) and *transference-focused therapy* (dysfunctional relationships are examined within the transference and the patient is taught to reflect) are some other approaches.

¹⁸⁶⁶ DSM-IV-TR criteria for **intermittent explosive disorder** (IED) include several discrete episodes wherein the person fails to control aggressive impulses that lead to (verbal or physical) assault or property damage; aggression is grossly disproportionate to any precipitant ('provocation' is usually from a known person); and there is no other explanation for these episodes. Comorbidity with anxiety, mood, eating, substance, other impulse control, and personality disorders (especially borderline and antisocial) is common. However, IED may antedate many of these disorders. Whilst IED is not commonly diagnosed some authorities insist that it is common, although high comorbidity levels may cloud the issue.

¹⁸⁶⁷ **Kleptomania** refers to compulsive stealing with increased tension before the act that is released by the act; unwanted goods are returned or thrown away. Mullen and Sullivan (2007, p. 492) are sceptical about this being a real disorder. The lifetime prevalence of shoplifting in the US is 11.3%. It is associated with illegal money making, scams aimed at extracting money from others, and disorders involving poor impulse control such as antisocial personality disorder, drug abuse, pathological gambling, and bipolar disorder. (Blanco et al, 2008)

¹⁸⁶⁸ **Pyromania**: *Monomanie incendiare* was described by a French psychiatrist, Charles Chretien Henry Marc (1771-1841), in 1833 and this was translated in English as pyromania. These rare people, males more than females, set fires deliberately. It cannot be explained by another disorder, impaired judgement (e.g. dementia), ideology, revenge, or criminality. Pyromaniacs are fascinated by fire, are fire-watchers, and, despite often not caring about the consequences of fires, may volunteer to help put out fires. Insight is poor, alcoholism is common, and patients often will not accept responsibility for their actions. Comorbid diagnoses include substance use disorder, ADHD, mood disorders, and pathological gambling.

prisoners, and the fathers of those with PG: modelling and identification are probably operative, although there may be some genetic input. Women may start gambling later than men, but there seems to be no significant difference between the sexes in terms of the age at presentation for treatment. Gambling increased significantly in the UK after the 1994 introduction of a national lottery, especially among those who could least afford it. Pathological gambling was increased in those living within 50 miles of a US casino. (Gould & Sanders, 2008, p. 310) Gambling is a more socially accepted outlet in some areas of society than in others. Women tend to gamble at different activities to men, e.g. bingo versus poker. Internet gambling is a novel problem. (Dineen, 2002) Only a minority of gambling is clinically pathological. Normal gambling is neither uncontrolled nor irresistible. It is abnormal if the gambler or his family view it as excessive; it is the sole relief from tension; the practitioner is preoccupied with it; there is loss of control over the amount gambled; and, if any important sphere of life (in gambler or dependants) is adversely affected. Viewed thus, it seems closely allied to alcoholism. Indeed, people with PG are at increased risk for alcoholism and other substance dependence. (Scherrer ea, 2005; Slutske ea, 2005) Adolescent-onset gambling may be particularly associated with present or later substance use disorders. (Lynch ea, 2004) Interruption in gambling leads to restlessness, irritability, and physical (e.g. alimentary) symptoms. Low mood and self-harm may follow depletion of family funds. Gambling offers a dissociative high that permits escape from mundane concerns. Pathological gambling might start when a (perhaps psychologically vulnerable) person observes others gambling and be maintained by variable ratio reinforcement scheduling. Addictive or impulsive behaviour in general may involve increased dopamine and noradrenaline activity and a reduction in serotonin¹⁸⁶⁹. Dopaminergic drugs (e.g. pramipexole) for Parkinson's disease and deep brain stimulation may trigger gambling activity¹⁸⁷⁰ that may respond, among other things, (Wong & Steiger, 2007) to a reduction in the dose of the offending agent or to risperidone. (Dineen, 2002)

Moran's (1975) classification of gamblers

Symptomatic - secondary to other psychiatric problems, especially depression – there is evidence for overlapping genetic factors for gambling and depression (Potenza ea, 2005)

Psychopathic - one part of an antisocial profile

Neurotic - secondary to stress, interpersonal or emotional difficulties

Impulsive - loss of control once a binge starts

Management ideally involves a full assessment of all aspects of the case by a multidisciplinary team. The spouse should be involved early. Discussion, advice, and treatment of any treatable disorder follow. Family support and/or therapy may be required. Psychotherapy (CBT) and a behavioural programme may be indicated. Desensitisation in imagination appears to be beneficial. The relaxed patient imagines a hierarchy of situations leading to gambling and then imagines leaving the scene without gambling. Controlled gambling is sometimes offered as an alternative strategy to abstinence, although, as with alcoholism, it is by no means certain how to predict who is likely to benefit. Motivational interviewing may help some people to quit. Combined imaginal desensitisation plus motivational interviewing may be successful, including for those who fail to respond to Gamblers Anonymous (GA). (Grant ea, 2009) SSRIs, naltrexone, and nalmefene (25 mg/day, an opioid antagonist: Grant ea, 2006) are other suggested methods of treatment. Gambling in people with 'bipolar spectrum disorders'¹⁸⁷¹ may be reduced with lithium (Hollander ea, 2005) or the anticonvulsants. There are many methodological problems to be considered in evaluating such research, particularly the small numbers involved.

GA¹⁸⁷² offers long-term support. Like Alcoholics Anonymous (AA), GA teaches an illness model and the necessity for abstinence; like AA, it employs public confession, peer pressure, and utilises reformed gamblers to help novices. GAM-ANON is for the relatives and friends of gamblers.

¹⁸⁶⁹ 5-HT is involved in initiating behaviour and behavioural disinhibition. Noradrenaline is important in being prepared for stimulation whereas dopamine is concerned with reward and reinforcement.

¹⁸⁷⁰ Pathological gambling in Parkinson's disease has a prevalence of 3.4%, rising to 7.2% in patients taking dopamine agonists.

Hypersexuality may also occur.

¹⁸⁷¹ I.e. subclinical or subthreshold cases.

¹⁸⁷² Founded: Los Angeles, 1957.

Ultimately, pathological gamblers must accept responsibility for debts. They should not have credit cards and it may be better if a responsible other handles their finances. Prognosis is often seen as poor, even with GA involvement, and there is a very high dropout rate from GA. Nevertheless, GA is a relatively strong force for change. Many give up gambling without any formal treatment. (Slutske, 2006) Prevention involves an unpopular strategy: reducing gambling outlets.

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15

Eating disorders

Brian O'Shea

'We each day dig our graves with our teeth'. Samuel Smiles (1812-1904), 1880.

It appears most likely that eating disorders are triggered by socio-cultural and interpersonal stressors and may then be sustained by neural networks including those subserving homeostasis (brain stem/hypothalamus), drive (mesolimbic cortex/striatum), and self regulation (top-down control that views appetite in terms of the wider context of goals, values, and meaning).(Treasure ea, 2010) Individual symptoms, such as purging, are far more common than the disorders themselves, and there is a strong argument for a spectrum viewpoint rather than a collection of discrete conditions. Overlap syndromes and subtype changes over time in individual patients are common.(Milos ea, 2005) Patton ea (2008) found partial eating disorder syndromes (at least 2 DSM-IV criteria for anorexia or bulimia nervosa) in 9.4% of 15-to-17 year-old females and 1.4% of males in the community; few progressed to full syndromes but depressive and anxiety symptoms, substance abuse, and retention of low weight into the mid-20s were common. Many cases of anorexia nervosa graduate to bulimia nervosa, whereas movement in the opposite direction is less common.(Eddy ea, 2008) The DSM-IV diagnosis 'eating disorder not otherwise specified' is applied to almost one-half of eating disorder patients seen at tertiary care levels.(APA, 2002, p. 741; Palmer, 2004) ICD-10 (F50) recognises typical and atypical forms of bulimia nervosa and anorexia nervosa, overeating or vomiting associated with 'other psychological difficulties', and the usual ragbag categories ('other' and 'unspecified'¹⁸⁷³). Eating disorders (threshold and below) are not uncommon in adolescent females who have type I diabetes mellitus, and these patients are prone to omitting insulin in the hope of losing weight.(Jones ea, 2000) Lower birth weight and poorer weight gain in early childhood may augur negatively for psychological outcomes in both adolescence and adulthood.(Cheung ea, 2002)

Feeding disorder of infancy or early childhood

DSM-IV-TR diagnostic criteria for this disorder describe persistently inadequate food intake with resultant weight loss or failure to put on weight. There is no detectable medical or other psychiatric (e.g. rumination) explanation. Food is readily available. Onset is before age 6 years¹⁸⁷⁴. The child gags, does not open its mouth, or may eat excessively slowly. Older children may demonstrate interpersonal problems, developmental delay, mood and behaviour difficulties, strange food choices, or eat in odd ways. Foraging for food may be noted. Various explanations have been proffered: homeostatic dysregulation (autonomic instability), problems of attachment¹⁸⁷⁵, painful oral medical procedures, child abuse, or maternal/family psychopathology. Outcome ranges from full spontaneous recovery to death. Treatment approaches may include behavioural, cognitive and educational elements.

Psychological (psychosocial/deprivation) dwarfism (psychological/psychosocial/maternal deprivation, feeding disorder of poor care giver-infant reciprocity)
Described by Powell and others in 1967

¹⁸⁷³ EDNOS (atypical eating disorders) or 'eating disorder not otherwise specified' includes BED or binge eating disorder. EDNOS is the most common eating disorder diagnosis.(Shafran ea, 2008, p. 629)

¹⁸⁷⁴ Another classification is: **non-organic failure to thrive** if the condition commences before the third birthday, and, when it starts later, **deprivation dwarfism** or **psychosocial short stature syndrome**. Not all cases of non-organic failure to thrive become psychosocial dwarfs.

¹⁸⁷⁵ E.g. carer does not provide adequate emotional nurturance or a power struggle.

Can be due to pica¹⁸⁷⁶ or inadequate nourishment
 Low growth hormone levels
 Child is of short stature
 Unusual eating habits are common
 Lack of engagement with care giver during feeding, e.g. no babbling
 Retarded speech development
 Temper tantrums may be a problem
 Tend to come from disturbed families
 Domestic physical abuse is not uncommon
 Separation from family is followed by normalisation of pituitary function

Hyperphagic short stature syndrome (Skuse ea, 1996)

Aberrant, bizarre behaviours
 Adverse home environment
 Linear growth failure
 Simulation of hypopituitarism
 Clears up when the child is removed from the home environment
 Similar reports date to 1960s

Kaspar Hauser syndrome

Sobriquet covering psychosocial dwarfism, affect hunger, retarded growth, intellectual deficits etc (Money, 1992)

Kreigsneugeborene ('war infants': Lawrence, 2006, p. 263)

German infants experiencing starvation during WWI
 Underdeveloped
 Restless
 Automatic grasping

Prader-Willi syndrome (Holland ea, 2003)

1:28,000 births and 1:52,000 of population
 Absent of paternal genes at 15q – usually part of the chromosome but less often both chromosome 15s are of maternal origin – the latter, called maternal disomy, is associated with greater later risk of psychosis
 Main psychiatric disorder is atypical affective disorder +/- psychotic features, possibly related to maternal uniparental disomy (Soni ea, 2008)
 Hypotonic neonate, delayed milestones, short stature, small hands/feet, dysmorphic facies, hypogonadism (with risk of osteoporosis)
 Tantrums, OCD, stubborn/possessive, skin-picking
 Increased pain threshold and reduced likelihood of vomiting and unusual temperature regulation may lead to missed physical illness
 Hyperphagia, which may be fatal

WAGR syndrome

1:500,000-1,000,000 people
 Wilm's tumour, aniridia, genitourinary problems, and mental retardation
 Deletions on chromosome 11p3
 Some cases have hyperphagia and obesity - BDNF haploinsufficiency is associated with low serum BDNF and childhood-onset obesity (Han ea, 2008)

The use of enteral feeding methods (NG tube, etc) in infants may increase resistance to taking food by mouth. It should be employed sparingly and an effort should be made to continue oral feeding. (Olson ea, 2008, p. 758)

¹⁸⁷⁶ Can be bizarre, e.g. eating garbage or drinking toilet water.

Rumination is usually a disorder of infancy (especially when alone) and the intellectually disabled (in whom it is more likely to persist), although it can occur in older children and adolescents in the absence of co-morbidity. Physical problems should be ruled out. The child voluntarily regurgitates its food into the mouth, as if chewing the cud. The food is then spat out or re-chewed and swallowed. The practice is most often enjoyable. Typical cases commence between 3 and 12 months of age and dies out by 36 months. Aetiological theories include self-pleasing¹⁸⁷⁷ and a method of catching the attention of caregivers. Weight loss, malnutrition, dehydration, aspiration, and even death may follow. Reactive parental distress may interfere with rearing. Diaphragmatic breathing should be encouraged as it disrupts ruminative behaviour. Putting a drop of lemon juice on the tongue each time the child regurgitates may reduce the incidence of this behaviour if the practice is maintained for long enough. Behavioural methods of treatment are popular, e.g. giving more attention or, in the case of very dangerous rumination in the intellectually disabled, mild shocks used in a contingent fashion. The domestic environment and child-caregiver interaction may need to be addressed. Psychopathology in the caregiver should be treated.

Pica: The ingestion of non-foods (inedibles) such as dirt, clips, cigarette butts, or paint carries a risk of poisoning, such as plumbism.(O'Shea, 2000) The child may be experiencing emotional stress. Intellectually disabled subjects are at high risk. Pica is common in children with sickle cell disease.(Ivascu ea, 2001) Pica can occur in pregnant women¹⁸⁷⁸. Pica is often associated with other behaviour problems and there is an excess of associated cerebral damage or intellectual disability. The latter patients include the most persistent cases of pica. Prevention is critical. In some developing countries soil (geophagia) may be eaten to curb diarrhoea or quench hunger. Some inner city folk who cannot get the type of soil they were used to in the countryside may eat laundry starch. Complications of pica include lead poisoning (e.g. paint) and parasitic infestation (faeces, soil). Intervention in pica is largely behavioural, e.g. limiting availability and response prevention.

Child stunting (linear growth failure secondary to pre- and post-natal poor nutrition and infection) in Indonesia is reduced by better parental education. Such parents are more likely to practice protective measures such as giving vitamin A, completing childhood immunisations, provide a cleaner environment, and use iodised salt.(Semba ea, 2008) Maternal education could mediate such protective practices via greater decision making power, higher IQ, and lower maternal depression levels, all interacting in a complex manner.(Wachs, 2008)

Food fads

These are only important if they become persistent and marked. The excesses of TV ('junk') meals eaten today may account for at least part of the disturbing increase in the incidence of obesity among teenagers.(Jain, 2004)

Obesity

'The only medical benefit of obesity is seen in osteoporosis, where bone density increases in response to increased mechanical stress'.(Hanlon ea, 2006, p. 111)

Obesity has always stalked humanity.(Haslam & Rigby, 2010)¹⁸⁷⁹ Obesity is, however, increasing at an alarming rate throughout the developed and developing world,(Crawford, 2002; Jain, 2004) including in children (Kipping ea, 2008), despite some hopes of a reversing trend.(Lobstein, 2008) Obesity is overrepresented in people with mental disorders in some but not all studies and, in a study of London civil servants, this association becomes stronger with age.(Kivimäki ea, 2009) Obese children and adolescents are at increased risk as adults for coronary heart disease¹⁸⁸⁰.(Baker ea, 2007; Bibbins-Domingo ea, 2007; Ludwig, 2007) Estimated US health costs for obesity are enormous: direct costs amounting to 7% of health care budget in 1995 (\$50 bn) and rising to \$98 bn (plus \$241 bn indirect costs) in 1997.(Wirshing & Meyer, 2003, p. 36) Estimated US health costs for obesity (2 out of 3 adults) and being overweight (1 in 5 children) in 2009 was \$147 bn.(Anonymous, 2009) WHO estimated (Groves, 2006) that obesity in Europe accounted

¹⁸⁷⁷ Other associated self-soothing behaviours include body rocking, head banging, and thumb sucking.

¹⁸⁷⁸ Some pregnant women eat ice and become anaemic. Both the anaemia and the ice consumption may respond to iron.

¹⁸⁷⁹ Obesity among patients in psychiatric institutions has been noted for many years, e.g. Charles Dickens noted recorded this phenomenon among patients resident for a matter of weeks during the 1850s.(Arnold, 2008, p. 213)

¹⁸⁸⁰ Other complications of childhood obesity: precocious puberty, low self esteem/social isolation/educational problems/low exercise tolerance, eating disorders, anxiety/depression, asthma, sleep apnoea, constipation, glomerulosclerosis, back pain/flat feet, fracture of forearm, Blount's disease (tibia vara – lower leg angles inwards), slipped capital femoral epiphysis, GORD, steatohepatitis, cholelithiasis, hypertension/coagulation problems/endothelial and inflammatory problems/dyslipidemia/type II diabetes.

for 6% of direct health costs and over 12% in indirect costs (foreshortened lives, decreased production, and reduced earnings). Haslam and James (2005) estimated that 30,000 people died annually in the UK (one-tenth of the US figure) from obesity.

Quételet's¹⁸⁸¹ body-mass index (BMI) = weight in Kg/height in metres² (Kg/M²)
 Grades 0, 1, 2, and 3 obesity corresponds to BMI values 20-25, 25-30, 30-40 ('clinically relevant'), and 40+ ('crippling') respectively
 The body's energy expenditure is made up of BMR (73%), thermogenesis (15%) and physical activity (12%)
 BMI inappropriate measure in childhood/early adolescence (needs to be corrected for age followed by reference to weight for height for age tables) and athletes (increased muscle mass yields high BMI no due to increased adiposity)

The epidemiology and prognosis of the eating disorders are summarised below in table form. Parents are poor at recognising obesity in themselves¹⁸⁸² (Morgan ea, 2008) and in their children.(Jeffery ea, 2005) Obese people often blame their 'glands' or 'genes'. Obese people have increased concentrations of insulin and cortisol in their serum and decreased plasma growth hormone levels, but these are probably due to being obese since they normalise when weight is lost. Wahrenberg ea (2005) found that a waist circumference of less than 100 cm excludes insulin resistance in both sexes. Montgomery and Ekblom (2002) reported an increased risk for diabetes and obesity among the offspring of women who smoked during pregnancy. Hypothyroidism, hypogonadism, hypopituitarism, and Cushing's syndrome are associated with obesity among other things. Maternal obesity is one risk factor for stillbirth.(Smith & Fretts, 2007) Clifford (2003) reviewed the literature on the connection between having been breast-fed (or not) and later obesity (or its absence) and found the evidence to be inconclusive. Obese children and adolescents appear to have relatively short sleep time, a core aspect being reduced REM sleep.(Liu ea, 2008) Also, children with poor hand control and coordination and who are clumsy may be more likely to be obese as adults.(Osika & Montgomery, 2008)

Multiple peptides contribute to increase or decrease food intake at the level of the hypothalamus. The characterization of an obesity gene (*ob*) on chromosome 6 in mice (and its human homologue) was reported in 1994. It was hypothesised that the *ob* gene on chromosome 7 produced an *ob* protein (this turned out to be leptin¹⁸⁸³) that acted on brain *ob* receptors leading to satiety and a reduction in food intake. It was later suggested that overexpression of the *ob* gene (and an increase in its mRNA) in adipose tissue might account for obesity in humans.

In fact, in excess of one hundred genes have been implicated in the determination of body weight. These act mainly through the brainstem and hypothalamus and influence food intake and tendency to exertion. For example, the melanocortin 4 receptor (MC4R) conveys food intake-suppressing and energy expenditure-increasing signals from the hypothalamus. SNPs in the fat mass and obesity-associated gene (FTO) influence adiposity, energy intake, and preference for foods of high caloric density (Leibel, 2008); FTO is highly expressed in brain and appears to influence brain volume.(Hoa ea, 2010) An extension of the Framingham Heart Study (DeBette ea, 2010) suggests that as BMI/visceral fat rises brain volume decreases in healthy middle-aged people. Lindgren ea (2009) performed a meta-analysis of 16 genome-wide association studies and identified two loci strongly associated with measures of central adiposity that mapped near TFAP2B and MSRA, whilst a third locus (near LYPLAL1) was associated with waist-hip ratio in women only.

Leptin ('*ob* protein?'; Gk: *leptos*, thin) levels are chronically elevated in obese humans. Apart from the few people with inherited leptin deficiency, therapeutic leptin use failed to work. According to Watts (2007) cells produce leptin to prevent too much weight loss during lean times rather than to prevent obesity!

Leptin

¹⁸⁸¹ Lambert Adolphe Jacques Quételet (1796-1874), Belgian astronomer, mathematician, statistician, and sociologist.

¹⁸⁸² E.g. self-reported BMI in Ireland in 2007 was lower than measured BMI for overweight and obese men and women.(Morgan ea, 2008)

¹⁸⁸³ **Leptin**, found in murine and human plasma, is a 16-kd protein. When injected into the peritoneum it causes a reduction in feeding and an increase in energy output. Lack of the *ob* gene causes obesity whereas leptin decreases body fat. (see box)

An interleukin 6 cytokine and a product of fat cells
 Reduces food intake, decreases insulin levels, and lowers blood glucose concentration in the ob/ob (obese) mouse but not in the db/db (mutant diabetic) mouse
 Leptin might exert its central effects via neuropeptide Y (NPY), a very powerful orexigenic¹⁸⁸⁴ peptide. Leptin inhibits NPY and agouti gene related peptide (Agrp) expression
 Central administration of NPY induces feeding and rest¹⁸⁸⁵
 A certain threshold of weight or body fat may be required for normal pulsatility of gonadotrophin-releasing hormone, but the underlying mechanism is unknown
 Leptin may help regulate reproductive function and signal the hypothalamus when fat mass is reduced. Leptin levels are reduced in underweight anorexia nervosa patients but these normalise with restoration of weight (Halmi, 2003, p. 1003)
 Alpha-melanocyte stimulating hormone¹⁸⁸⁶ reduces appetite and leptin stimulates α -MSH production
 Mouse and human melanocortin receptor gene mutations lead to hyperphagia and obesity; α -MSH is an agonist at this receptor
 A fall in food intake \rightarrow decreased leptin \rightarrow increased NPY/Agrp + reduced POMC activity \rightarrow inhibition of GABA interneurons \rightarrow increased appetite (Connan, 2002)
 A deficiency of leptin acts as a defence against starvation (this seems to be its primary role)

YY₃₋₃₆ (also called PYY₃₋₃₆), a peptide hormone, is produced by the intestine after a meal. It inhibits neuropeptide Y (a powerful appetite stimulant) in the arcuate nucleus of the hypothalamus¹⁸⁸⁷. Injections of PYY₃₋₃₆ in humans leads to a reduced consumption of calories over the following 24 hours (Batterham ea, 2003) and a single intraperitoneal injection of the same substance can reduce food intake for up to a week in rats. Korner and Leibel (2003) warn about extrapolating from single injects: the development of antibodies or tachyphylaxis through receptor downregulation may limit the efficacy of prolonged PYY administration.

Bilateral ablation of the lateral hypothalamus¹⁸⁸⁸ causes anorexia and loss of weight, whilst destruction of the paraventricular nucleus leads to hyperphagia and obesity. Galanin is an orexigenic peptide that probably acts at the level of the paraventricular nucleus. The latter nucleus also contains anorexigenic peptides such as TRH and CRH.

Cocaine- and amphetamine-regulated transcript (CART) may be part of the anorexigenic system of the arcuate nucleus. CART neurones are stimulated by leptin.

Peripheral produced CCK suppresses eating by acting on the vagus nerve and activating hind brain circuits. (Konsman & Dantzer, 2002)

Orexins/hypocretins¹⁸⁸⁹, discovered in 1998, are neuropeptides produced in the lateral hypothalamus ('feeding centre'). The latter sends projections throughout the CNS. Orexins stimulate feeding and may have a role in narcolepsy.

In animals, cannabinoid-1 receptor (CB1) blockade produces a lean phenotype that protects against obesity related to diet and its associated dyslipidaemia. There was evidence in humans that the selective CB1 blocker rimonabant¹⁸⁹⁰, combined with a low calorie diet, promotes decrease of bodyweight and waist circumference and improvement in cardiovascular factors. (Van Gaal ea, 2005)

¹⁸⁸⁴ Increases appetite, i.e. opposite to anorexigenic.

¹⁸⁸⁵ It needs to be given repeatedly to cause significant gain in weight.

¹⁸⁸⁶ α -MSH – derived from POMC.

¹⁸⁸⁷ Destruction of the arcuate nucleus leads to hyperphagia and obesity: if the arcuate nucleus is destroyed there is no response to leptin.

¹⁸⁸⁸ A major site of expression of the orexigenic melanin concentrating hormone.

¹⁸⁸⁹ Gk. *orexis*, appetite.

¹⁸⁹⁰ **Rimonabant (Acomplia) had its European marketing authorisation suspended by the European Medicines Agency in 2008 because of associated depression.** It is a selective CB1 cannabinoid receptor blocker that is said to reduce weight and weight circumference, improve glycaemic control (HbA 1c), increase HDL-c, and reduce triglycerides (Anonymous [2007] was critical of the degree of such changes). It was indicated as an adjunct to diet and exercise for obesity or overweight adult (> 18 years) patients with associated risk factors, e.g. type II diabetes or dyslipidaemia. (Scheen ea, 2006) Caution was required in cases of moderate liver impairment or epilepsy, and it was not recommended in the presence of severe hepatic or renal impairment. It should be avoided in uncontrolled serious psychiatric disorder and it was not recommended for people on antidepressants. In 2007 FDA has warned of an increased risk of depression and suicide with rimonabant and, despite depressed mood being an exclusion criterion in trials, Christensen ea (2007) found in their meta-analysis that 20 mg/day rimonabant increases the risk of depression and anxiety (The endogenous cannabinoid anandamide has an antidepressant-like effect in rodents, an effect blocked by rimonabant: see Mitchell & Morris, 2007). Rimonabant contains lactose. CYP 3A4 inhibitors like ketoconazole increase plasma rimonabant levels, whereas inducers of CYP 3A4 (St John's Wort, carbamazepine, etc.) reduce plasma rimonabant levels. It was not recommended during pregnancy and is contraindicated during breastfeeding.

Peroxisome-proliferator-activated receptor (PPAR, especially PPAR δ) activates metabolism and appears to decide if body cells store or burn fat. Mice whose gene for PPAR δ remains in the 'on' position put on less weight than other mice. (see Wang ea, 2003; Watts, 2007)

The psychological routes to obesity include responses to depression¹⁸⁹¹, anxiety, boredom or other unwelcome affects. Social or cultural factors may moderate or mediate the association between obesity and mood disorder. (Simon ea, 2006) According to the Framingham Heart Study, a person is 57%, 40% and 37% more likely to become obese if his/her friend, adult sibling or spouse becomes obese respectively¹⁸⁹². (Christakis & Fowler, 2007) Nocturnal eating, nibbling between meals, and eating the wrong food¹⁸⁹³ and other bad habits play a role, as does alcohol. Unresolved dynamic-neurotic factors and learning theory are generally considered to be operative. Severely obese people may have low self-esteem. Volkow and O'Brien (2007) point out that DSM-IV does not recognise obesity as a psychiatric disorder and offer a list of behaviours for this 'food addiction'.

Suggested psychiatric criteria for obesity (Volkow & O'Brien, 2007)

Need to eat more to be satisfied (tolerance)
 Dieting-associated distress/dysphoria
 Eats more than intended
 Always wants food and can't curtail amount consumed
 Avoid activities because of fear of rejection due to obesity
 Overeats despite knowing of ill effects and psychological sequelae

Clouston, in 1881, wrote that fattening a patient would improve the mental state. In the 1980s it was noted that haloperidol seemed to put on less weight than other neuroleptics, a finding attributed to more selective DA blockade. Around the same time, it was suggested that perhaps 5-HT receptor blockade in the hypothalamic satiety centre¹⁸⁹⁴ greatly increased appetite for food. The TCAs, MAOIs and lithium tend to cause weight gain. Direct intra-hypothalamic injection of chlorpromazine in animals leads to an increase in food intake.

Morbid obesity provides an increased reservoir for psychotropic drugs with persistence of the effects of such drugs. (Janicak ea, 1997)

Apart from the well known physical complications of obesity¹⁸⁹⁵ there is evidence that obesity is associated with in the risk for almost all cancers, (Calle ea, 2003, 2007; Renehan ea, 2008) including colon, rectal, and pancreatic cancer in males and endometrial¹⁸⁹⁶, non-Hodgkin's lymphomas, and ovarian¹⁸⁹⁷ in females¹⁸⁹⁸. Animals that have their food intake restricted have less cancer than do animals allowed to eat as much as they wish. Adami and Tichopoulos (2003) felt that the risk of cancer from obesity is small relative to the effects of smoking, a view not shared by Haslam and James¹⁸⁹⁹. (2005) Possible ways in which obesity

Very common – nausea, upper respiratory tract infection

Common – gastroenteritis, depression, anxiety/irritability/nervousness, sleep disorders, memory loss, hypoaesthesia, sciatica, hot flushes, diarrhoea, vomiting, itching, sweating, tendonitis, muscle cramps/spasms, asthenia/fatigue, influenza, falls/bruises/joint sprains

Uncommon – panic, anger, 'dysphoria', 'emotional problems', lethargy, hiccups, night sweats

Rare – hallucinations

¹⁸⁹¹ The relationship between obesity and depression may be reciprocal with depression leading to obesity and obesity causing depression. (Luppino ea, 2010)

¹⁸⁹² These effects were not seen among immediate neighbours.

¹⁸⁹³ E.g. 'fast-foods': Pereira ea. (2005)

¹⁸⁹⁴ A fall in glucose activates the lateral hypothalamus (LH) and activity within the LH gives rise to hunger. Glucose activates the ventromedial hypothalamus (VMH) and activation of the VMH causes a feeling of satiety and inhibition of further feeding. I.e. lateral hypothalamus = **hunger centre** and ventromedial hypothalamus = **satiety centre**.

¹⁸⁹⁵ Cardiovascular (Rich-Edwards ea, 2005), phlebitis, hypertension, respiratory, gall bladder disease, pancreatitis, diabetes, (non-alcoholic) fatty liver (disease), dyslipidaemia, cataracts, joint problems, skin disorders, gynaecological problems, gout, etc.

¹⁸⁹⁶ Endometrial hyperplasia occurs in the obese because there is increased aromatization of androgen to oestrogen in fat.

¹⁸⁹⁷ A large US study of women aged 50-71 found that obesity was associated with an almost 80% higher risk of ovarian cancer – the increased risk only applied to women who had never used menopausal hormone therapy and women with a negative family history for this malignancy. (Leitzmann ea, 2009)

¹⁸⁹⁸ It is estimated that 5% of all cancers in UK postmenopausal cancers are attributable to being overweight/obese. (Reeves ea, 2007)

¹⁸⁹⁹ These authors suggest that obesity overtook smoking as the leading preventable cause of illness and premature mortality.

might increase cancer risk include altered concentrations of insulin, insulin-like growth factors, and sex steroids leading to a change in the balance between cellular proliferation and apoptosis; altered metabolism of adipokines; localised inflammation; oxidative stress; changed immune response; hypertension¹⁹⁰⁰; lipid peroxidation; non-alcoholic fatty liver; and, because of abdominal obesity, gastro-oesophageal reflux.(Larsson & Wolk, 2008) Obesity shortens the telomere.(Valdes ea, 2005) Abdominal obesity, because of visceral¹⁹⁰¹ fat accumulation, may be a problem in elderly depressives.(Vogelzangs ea, 2008)

Pseudotumour cerebri

Raised intracranial pressure, papilloedema, visual loss, VI cranial nerve palsy

Headache, if present, is typically pulsating

Classically affects young obese women

Can be - *primary* (idiopathic intracranial hypertension)

- *secondary* (e.g. neoplasm, obstructed ventricles, cerebral vein thrombosis, cardiac failure, COPD, eclampsia, sleep apnoea, vitamin A and derivatives, tetracycline, lithium, corticosteroids withdrawal, renal disease, hypoparathyroidism, plumbism, Lyme disease, SLE, hypertensive encephalopathy)

Management of primary cases: weight loss, repeated lumbar puncture, diuretics, topiramate, emergency steroids or surgery (e.g. fenestration of II nerve sheath) to preserve vision

Pregnancy complications associated with obesity¹⁹⁰² (Stotland, 2009)

Reduced fertility

Congenital malformations¹⁹⁰³

First trimester spontaneous abortion and miscarriage

Large babies

Gestational diabetes mellitus

Hypertensive disorders (chronic hypertension or pre-eclampsia)

Prolonged labour

Unplanned caesarean delivery

Patients may have excessively optimistic expectations of each novel therapy.

Current criteria for using anti-obesity drugs are: BMI of at least 30 or BMI over 27 when co-existing conditions are present. Anti-obesity drugs do not cause particularly significant weight loss¹⁹⁰⁴ and have their own adverse event profile. The chief approach is a normal reducing diet: eat plenty of fibre and exercise regularly.(Lean ea, 2007; van Sluijs ea, 2007) A low calorie diet¹⁹⁰⁵ is prescribed. As long as the calorie content of the diet is reduced it doesn't seem to matter whether the emphasis is on protein, carbohydrate or fat when composing such a diet.(Sacks ea, 2009) Crash diets should be avoided. Obese people tend to eat more than they report during a diet and to overestimate physical activity. Self-monitoring, response prevention strategies to counter identified behavioural and cognitive cues, reinforcement, family or marital work, and psychotherapy are all useful in individual cases. Short term goal and self reward for various degrees of weight loss are critical. Follow up sessions may be needed during crises.

Severe diarrhoea, deficiency states, and renal problems may complicate surgery¹⁹⁰⁶, such as jejuno-ileal bypass, gastroplasty, and cholecystjejunostomy. Liposuction (fat removal by suction) may reduce weight (often temporarily), girth, and leptin levels in plasma, but it may not improve metabolic problems associated with obesity and therefore may not reduce the risk for coronary disease.(Klein ea, 2004)

¹⁹⁰⁰ It is important to use a large cuff when measuring blood pressure in a person with a large arm.

¹⁹⁰¹ Centrally located fat (particularly intra-abdominal) is more likely to be associated with severe abnormalities of serum lipids.

¹⁹⁰² 1 in 5 women were obese at their first antenatal visit at the Coombe Maternity Hospital, Dublin.(Barry ea, 2009)

¹⁹⁰³ Stothard ea (2009), in a meta-analysis, found that obese mothers had an absolute risk of having a baby with a neural tube defect or a serious cardiac anomaly was 0.47 and 0.61/1,000 births respectively greater than was the case for mothers whose BMI was in the recommended range.

¹⁹⁰⁴ Orlistat, sibutramine, and rimonabant reduce weight by less than 5 kg on average.(Rucker ea, 2007)

¹⁹⁰⁵ 800-1,000 K cal daily – lower levels may reduce BMR.

¹⁹⁰⁶ Bariatric surgery is the technical term for anti-obesity procedures. There is a small mortality risk in the short term and abdominoplasty may be required by many patients.(Arterburn, 2008)

Drugs such as T3, dinitrophenol and sympathomimetics can be toxic and are useless anyway. Central stimulants (phentolamine, diethylpropion, and amphetamine) act on adrenergic receptors causing central stimulation and may precipitate psychiatric problems.

Fluoxetine, an SSRI, is useful for binge eating. In acute treatment, fluoxetine and fluvoxamine may cause weight loss (at least in the short term), whereas citalopram, sertraline and paroxetine seem to be weight neutral.¹⁹⁰⁷ Nevertheless, the question arises that SSRIs when followed up for long enough may cause weight gain.(Sherman, 1998) Fenfluramine acts by releasing 5-HT. Fenfluramine could increase satiety rather than causing anorexia.¹⁹⁰⁸

Phentermine (Ionamin), an amphetamine derivative¹⁹⁰⁹, should not be given for longer than 6 months and is usually given for 4-6 weeks. Phentermine therapy should be adequately supervised and is not a first-line therapy. Side effects include headache, anxiety, insomnia, hypertension, bradycardia, and palpitations. It can cause pulmonary artery hypertension. Contraindications include pulmonary artery hypertension, severe systemic arterial hypertension (monitor BP in hypertensives and patients at risk of same), present or past cerebro- or cardio-vascular disease, a propensity for alcohol or substance abuse (not as big a problem as with other amphetamines), or children under 12 years of age. It should be avoided in the presence of current or past psychiatric disorder (including anorexia nervosa and depression). According to Eckel (2008) efficacy and safety data for phentermine are limited and there is a potential but low possibility of abuse.

Orlistat (Xenical), 120 mgs (capsules) tds with meals, used in conjunction with a low calorie diet¹⁹¹⁰, promotes weight loss by selectively inhibiting gastrointestinal and pancreatic lipase activity, so reducing dietary fat absorption by 30%. According to Anonymous (2007) orlistat (tetrahydrolipstatin) is the obesity drug with most evidence for efficacy and safety¹⁹¹¹. Xenical, which is not absorbed, is indicated if the BMI is 30 or more. It is said to decrease LDL cholesterol more than does diet alone. It reduces the LDL: HDL cholesterol ratio, to decrease fasting plasma glucose and insulin concentrations to improve glycaemic control, and it may offer some protection against the development of type II diabetes mellitus. Some concern has been expressed over an association between orlistat and hypertension.(Persson ea, 2000) It can cause faecal incontinence and urgency, oily spotting, and flatulence.(Noël & Pugh, 2002) There is a potential for malabsorption of fat-soluble vitamins.(Hanlon ea, 2006, p. 115)

Sibutramine, (Reductil) is a MAOI which increases noradrenaline peripherally at beta-3 receptors¹⁹¹² and causes weight loss by heat production and increased consumption of oxygen. European regulators suspended marketing authorisation for sibutramine and the FDA placed restrictions on its licence because of concerns about raised risks of heart attacks and CVAs.(Sayburn, 2010; Williams, 2010)

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue that can be given subcutaneously and may hold promise in the treatment of obesity.(Astrup ea, 2009)

Naltrexone plus bupropion combination treatment (Greenway ea, 2010) may have a role in treating overweight and obese adults. The commonest adverse effect is nausea, others including headache, dizziness, constipation, vomiting, and dry mouth being less common. Most obese patients do not need medical help to lose weight and most will drop out from treatment.

Yanovski and Yanovski (2002) remind us that the main approaches to the treatment of obesity are behavioural (improved diet and increased physical activity) with weight-loss medications reserved for patients at substantial risk because of their obesity and where non-drug treatments have failed. In motivated patients, the aim is to achieve gradual and modest weight loss by caloric restriction, physical activity, and behavioural treatments.(Noël & Pugh, 2002) Promotion of cycling is practical step advocated by Lavery.(2008)

¹⁹⁰⁷ Of course, SSRIs should be given with food to reduce GIT side effects!

¹⁹⁰⁸ It could be associated with depression if suddenly withdrawn. It was contraindicated in those patients with a psychiatric history. Other associated problems included nausea, diarrhoea, lethargy, dyspnoea (pulmonary hypertension), and increased dreaming. Diethylpropion (adrenergic stimulant that releases brain noradrenaline) was removed from the Irish market in 1995 because it was being abused and can also cause pulmonary hypertension. Anorectic drugs like phentermine, diethylpropion, fenfluramine, and D-fenfluramine can cause a serotonin syndrome if given in conjunction with a MAOI. Servier (Ireland) voluntarily removed fenfluramine and dexfenfluramine from the market in 1997 because of reports of heart valve lesions. Similar withdrawal occurred in Europe.

¹⁹⁰⁹ Like diethylpropion, this is an adrenergic stimulant that releases brain noradrenaline and reduces food intake.

¹⁹¹⁰ Some authors wonder if the accompanying low-fat diet (which reduces side effects) is actual the active therapy.(Hanlon ea, 2006, p. 115)

¹⁹¹¹ Orlistat was approved by the FDA in the US for use over the counter in 2007.

¹⁹¹² It is also a serotonin reuptake inhibitor. It was contraindicated in the presence of psychiatric disorder, coronary artery disease, congestive heart failure, or a blood pressure greater than 145/90. It was licensed for use in the treatment of obesity for a period of one year. It was effective in the treatment of patients with binge-eating disorder in a number of studies.(Appolinario ea, 2003; Wilfley ea, 2008) If taken with diet and support it reduces weight by 5-7%.(Anonymous, 2001) However, weight is quickly regained when sibutramine is stopped. It can cause dry mouth, constipation, insomnia, tachycardia and hypertension and it potentially interacts with drugs affecting cytochrome P450 3A4 and those increasing serotonin levels. One reviewer (Anonymous, 2001) described it as 'difficult and impractical to use' and of 'limited potential benefit'. Reports from around the world of sibutramine-related fatalities prompted Italy to suspend sales and other countries to initiate reviews of the drug.(Noël & Pugh, 2002) Sibutramine (Clark & Harrison-Woolrych, 2004) and other 5-HT reuptake inhibitors, such as fluoxetine,(Joss ea, 2003) have been reported to be associated with memory impairment.

According to Noël and Pugh (2002), surgery for obesity¹⁹¹³ should be confined to patients who are at least 18 years of age who have a BMI of at least 40 or have a BMI of 35-40 with serious complications of obesity. Intensive, specialised interventions should have failed or there should be an inability to maintain weight loss with non-surgical approaches. There should be no contraindication to surgery or anaesthesia, and the patient must be willing to undergo long term follow-up. According to Mason (2003), opinion differs on the use of surgery for obesity and different procedures are employed in different countries. Wernicke-Korsakoff syndrome may follow bariatric surgery.(e.g. Foster ea, 2005) According to The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium (2009) adverse 30-day outcomes of surgery are related to a history of DVT, pulmonary embolus, obstructive sleep apnoea, impaired functional status, and extreme values of BMI.

Since **obesity** has become more common in genetically stable populations it must be of primarily **environmental origin** according to Ebbeling ea (2002)

Suggestions for tackling the problem

Breastfeeding (Groves, 2006)¹⁹¹⁴

Domestic - healthy meals (less salt, sugar, and fat) at fixed times, more activity, less TV¹⁹¹⁵

School - physical education, healthier food, no fattening food/beverages from vending machines

Town planning - encourage exercise¹⁹¹⁶ (Kimm ea, 2005); bicycles instead of cars (Groves, 2006)

Non-drug management of antipsychotic-induced weight gain¹⁹¹⁷, e.g. individual/group approaches, CBT, and nutritional counselling (Ávarez-Jiménez ea, 2008)

Better insurance cover for proven treatments for obesity

Marketing/media¹⁹¹⁸ - discourage bad foods, encourage good foods, clear labelling, and discourage advertisements aimed at youth

Politicians - no contributions from food industry

A major problem in tackling obesity is that many obese people may not see obesity as being a problem for them.(Johnson ea, 2008) Population changes in physical exercise and diet are the main culprits according to Kipping ea.(2008a,b) Education aimed at discouraging children from drinking carbonated drinks has led to weight loss in the short term only¹⁹¹⁹.(James ea, 2004, 2007) Such programmes may need to be sustained to have a persistent effect.

Epidemiology of eating disorders

<i>Year</i>	<i>Data</i>	<i>Comments</i>
Obesity		
1987	8% men, 12% women	British prevalence
1993	2nd cause of death after cigarettes	USA (McGinnis & Foege, 1993)
1994	9-10 year olds; 10 year follow up	Danish; parental neglect promotes obesity
2002	15 million people in US have BMI of 35 kg/m ² or more	This means 1 in 20 people
	16.7% boys, 15.4% girls	US prevalence
2004	32.7% of men obese	Japan Society for Study of Obesity

¹⁹¹³ E.g. adjustable gastric banding, Roux-en-Y gastric bypass, and sleeve gastrectomy. See Leff and Heath (2009) for a review.

¹⁹¹⁴ Groves (2006) was quoting WHO which brought European states together in November 2006 to initiate European Charter on Counteracting Obesity.

¹⁹¹⁵ According to the Kaiser Family Foundation in early 2010, children aged 8-18 years spend an average of 7.5 hours watching TV, playing video games, or listening to music on computers.

¹⁹¹⁶ Exercise improved motor skills but did not reduce BMI in young children in one trial.(Reilly ea, 2006) Irish adolescents may exaggerate the level of exercise taken.(Shiely & MacDonncha, 2009)

¹⁹¹⁷ Potentially all antipsychotics can induce weight gain. Weight gain develops rapidly.(Tarricone ea, 2010) Visceral obesity, a risk factor for metabolic syndrome, is the usual pattern. Weight gain should be monitored and interventions should be early. Some clinicians use anti-obesity drugs and behavioural approaches. Entrance into a 'wellness programme' may help. Many clinicians switch to a different antipsychotic, e.g. aripiprazole or ziprasidone.

¹⁹¹⁸ E.g. the *Change4Life* programme in Britain in 2009.(Mayor, 2009)

¹⁹¹⁹ Kipping ea (2008) suggest that the main things we can change in relation to children who are obese are gestational diabetes in the mother, amount of time in front of TV, level of exercise taking, parental inactivity, and amount of fat/carbohydrate/sweetened drinks imbibed.

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2006	1 in 5 Europeans obese 31.1% of men and 33.2% of women are obese in USA	WHO Non-Hispanic Blacks and Mexicans in US have very high rates
2007	2.7 comorbid medical diagnoses; 40.7% metabolic syndrome (F>M); 51% obese; 51% cholesterol > 5; prolactin raised in 2/3 females	Long-stay patients; GP input needed (O'Brien et al, 2007)
2008	Overweight children do not always become overweight adults No increase in childhood obesity between 2003/4 and 2005/6 Small fall in obesity in better off children Decrease in prevalence of overweight girls 22 million children in world are overweight Eating quickly and to fullness associated with obesity	Japanese, cross-sectional, retrospective of females* USA France Sweden 75% live in low/middle income countries (WHO) Japanese study
2009	In Europe general and abdominal adiposity are associated with increased risk of death Overweight/obesity has same risk for death as does smoking General population survey	Supports use of waist circumference or waist-to-hip ratio as well as BMI in assessing risk of death 46,000 Swedish late adolescent conscripts
	US obesity prevalence rose by 37% during 1998-2006 More than 70,000 new cancers annually in Europe related to excess body weight Mid-life adiposity reduces chances of good health in old age Common mental disorders increase obesity risk Obesity will outweigh effects of decline in smoking in US	Schizophrenia but not affective psychosis associated with obesity (Finnish study of people aged 30 years or more; results remain after controlling for medication, diet, smoking and education) 'Weight of the Nation' conference, Washington DC Especially endometrium, postmenopausal breast, and colorectal Study of US female nurses Study of London civil servants Obesity reduces life expectancy
2010	Objective activity reduces obesity in 12-14 year olds	England
Anorexia nervosa		
1989	7% of cases are male	
1991	13% of 16 year old schoolgirls score above cut-off on the EAT**; 4% took laxatives	Dublin
1995	Median prevalence of 1.3/1000 families AN not increasing in prevalence	Analysis of 29 cross-sectional surveys
1996	Clinic cases had excess higher social classes	Social classes evenly distributed in community
1997	Significant weight/shape concerns in girls: 11.5%, 11-12 year old; 14.9%, 12-14 year old; 18.9%, 15-16 year old	Significant ideational/behavioural disturbance in older group only
1998	Probably not associated with high social class but may be linked to education	Richard Morton (17th century) relieved a case by banning study!
2001	Recovery still possible after many years, but so is relapse	21-year prospective follow-up
2005	No change in incidence 1994-2000	Primary care setting (incidence 4.7/100,000 pop.)
2010	SMR [^] = 6.9 BP associated with excess of eating disorders (ED) in Italy Every other US child has BMI that is at least at 85th centile on age-specific national growth charts for ideal weight gain	Natural and unnatural causes of death more common in 20 years or more after first admission of females (retrospective Swedish register study) 148 patients (BP-I, BP-II, +/- cyclothymia): 31% had lifetime ED; AN = 15.5%; BED = 14.2%; BN = 5.4%; multiple EDs = 4.1% National Health and Nutrition Examination Survey
Bulimia nervosa		
1989	F:M ratio of 3:1	
1990	1% prevalence in adolescent/young adult women	USA
1992	1-2% of young adult women have it	Britain
2005	Incidence 6.6/100,000 pop.	Primary care setting
2006	Decline in point prevalence 1982-2002 in females at one US university	Not due to changed service use; may be explained by changing socio-cultural factors

*However, Japanese children may be less fat than Westerners; there may be social pressures encouraging weight loss; and young Japanese girls smoke more today than heretofore.

**Eating Attitudes Test. ^ SMR: standardised mortality ratio.

Prognosis in the eating disorders

<i>Year</i>	<i>Data</i>	<i>Comments</i>
Obesity		
2000	At least 1 in 3 Americans have weights at least 20% over desirable weight	50% US females & 25% US males dieting today, usually with little prolonged benefit (most put it back on)
2003	Obese elderly women at increased risk of dementia	18-year follow-up
2005	Obesity limited to childhood has little impact on adult outcomes; persistent obesity in women associated with poorer employment and relationship outcomes; persistence in men has no adverse outcomes	British birth cohort, part of 1970; 29/30 year follow-up
2005	Parental obesity, early BMI or adiposity rebound, > 8 hrs in front of TV at 3 years, catch-up growth. standard deviation score for weight at 8 months, weight gain first year, birth weight, and short sleep duration at 3 years predict childhood obesity	Prospective UK study
2006	Obese people at increased risk of dementia Obesity in middle age associated with increased risk of death	Follow-up from age 40-45 in 1960s/70s to mid-1990s in California US follow-up of people 50-71 years old
2009	BMI predicts mortality	Collaborative analysis of 57 prospective studies – higher BMI-related Deaths related to vascular disease; smoking important at lower BMIs
Anorexia nervosa		
1991	Poor outcome if later onset, neurotic or personality disturbance, dysfunctional family, longer illness	UK 20 year follow-up
1995	Mortality rate in AN higher than in female psychiatric patients or general population	Meta-analysis
1997	Early-onset: half recover by 2 years	Healthy family function and precipitating life events = good short-term outcome (lose predictive power at 2 years because of improvement in other cases)
1998	10% still have AN after 10 years; rest have low weight and cognitively AN, e.g. perfectionist; depression, alcohol abuse & anxiety common	Females attending special clinic during early 19980s v controls
1999	Specialty inpatient units have better outcomes	More expertise and experience than general inpatient settings
2002	½ recover, 1/3 improve, 1/5 chronic	Review of 2nd half 20th century; better outcome with younger onset & longer follow-up, worse with vomiting, bulimia, purgation, chronicity, obsessional/compulsive personality
2006	Mortality rate improved from 4.4% to 1.3% in hospitalised cases of AN	Swedish register study of 2 adolescent cohorts born 1958-67 and 1968-77 – due to specialist units?
2006	Mortality rate of 1.2%	Swedish study; born 1968-77; 9-14 year follow-up; 8.7% had persistent psychiatric problems requiring hospital care; 2.4% required public financial assistance
2007	33% full recovery at 2 years; 27% Still with AN; out-patient treatment as good as in-patient treatment	Multicentre randomised controlled trial
2009	Teenage-onset AN 18 years post-onset	No deaths. 12% persistent eating problem (half of these had AN). 39% had at least 1 psychiatric disorder (often associated with no job). Poor outcome: premorbid obsessive-compulsive personality disorder, age at onset of AN, and autistic traits
Bulimia nervosa		
1991	Borderline personality disorder	Poor therapeutic outcome
1994	52% fully recovered, 9% had full syndrome, 39% had some symptoms	10 year follow up of 88% of sample
1994	31% relapse rate, especially in first 6 months	2 year follow up, female attenders, eating disorder centre, Toronto
1995	Decreased prevalence in both sexes and improved clinical profile	US college students, 1982-92

2002	4 months after CBT, 44% relapsed	Poor outlook if very preoccupied with/ritualise eating, less motivated, or shorter abstinence during treatment period
2004	Course & outcome of BN (purging type) generally better than for AN	12-year follow-up, females
2004	Early change in frequency of purging was best predictor of response at end of treatment and at 8-month review	CBT and interpersonal psychotherapy
2006	EDNOS 60%, BN 25.5%, AN 14.5%	Percentages of different eating disorders in a community sample
2009	45% full recovery, 27% considerable recovery, 23% chronic protracted course 22.5% cross-over to another eating disorder 0.32% crude mortality rate; other psychiatric diagnoses common; highest recovery rates at 4-9 years follow-up	EDNOS = eating disorder not otherwise specified 79 studies that varied in what they covered; lack of standardised outcome criteria
	2011 Crude mortality rates as % for AN, BN and EDNOS* = 4, 3.9, and 5.2 respectively	Treated at academic specialised centre

*EDNOS = eating disorder not otherwise specified.

Anorexia nervosa (AN)¹⁹²⁰

Epidemiology

The incidence is c. 1/100,000 of the population, although figures vary. The point prevalence for Britain was estimated by Crisp to be about 10,000 severe cases.¹⁹²¹ According to Morris and Twaddle (2007) the prevalence of AN is about 0.3% of young women, the average age of onset is 15 years, it is the commonest cause of weight loss in young women, and 80-90% of cases are female.

Clinical features

¹⁹²⁰ Sir William Withey Gull (1816-1890), the famous English physician, is credited with describing both myxoedema and AN, the latter in 1868 (as *aepsia hysterica*) -74 (as *anorexia nervosa*). 'AN' is a misnomer since loss of appetite is not one of its features. Gull actually acknowledged the French neuropsychiatrist Ernest Charles Lasègue (1809-1883) as having written about the condition ('hysterical anorexia') before him, and Richard Morton (1637-1698, the Englishman who stated that tubercles are always found in TB) published his account of 'nervous consumption' in 1694. The German name is *Magersucht*, meaning an addiction to being thin. Other names include 'chlorosis' and 'green sickness' (these terms also referred to anaemia; 'tropical chlorosis' referred to hookworm infestation in Egypt). 'Anorexia mirabilis' of Medieval Europe wherein a person with deep religious devotion practiced severe food restriction was seen as being non-pathological. Between 1914 and 1949 AN was confused with Simmonds' disease (Morris Simmonds, 1855-1925, described hypophyseal cachexia, i.e. hypopituitarism – Harold Leeming Sheehan, 1900-86, recorded cases of acute postpartum pituitary necrosis: Kovacs, 2003) and patients with AN were given pituitary extract! Heavy vinegar consumption was once a noted problem in AN. Did St Catherine of Siena (1347-1380) have anorexia nervosa? The last of 25 children, Catherine cut off her hair when her parents insisted that she marry. She is recorded as starving herself, bingeing, using a reed to induce vomiting, and employing herbs to purge herself. (Bell, 1985) Catherine, contrary to some written opinion, was literate.

¹⁹²¹ Claims for an increase in the incidence of AN may reflect an increase in the number of young women in the population and an increase in re-admission rates, (see Currin ea, 2005) rather than due to any real increase in risk, although some authors strongly believe that there has been a real increase. (Halmi, 2003, p. 1004) DSM-IV required a body weight of < 85% of that expected for age and height whereas DSM-III-R required at least 25% weight loss, a change that could itself cause a spurious increase in cases of AN.

AN consists of failure to eat, some type of body image disturbance, body weight of less than 85%¹⁹²² of that expected or BMI of 17.5 or less, and amenorrhoea¹⁹²³ of 3 or more months' duration (criteria vary). About 5% of cases are male. A BMI of 17.5 or less may indicate a case of anorexia nervosa. Denial of problems¹⁹²⁴ and depression are common. Low self-esteem, perfectionism and undue compliance are said to be common premorbid characteristics. Other possibilities include tomboyishness, excessive emphasis on big family meals¹⁹²⁵, and a premorbid 'ideal' child. Sufferers with AN are often socially withdrawn and may dream about food whilst starving themselves!

According to Cohen (2003, pp. 324-330) 95% of AN starts with normal dieting, the dieting then becoming out of control and autonomous. Up to three-quarters of cases report engaging in excessive exercise before starting to diet.¹⁹²⁶ The problem here is that the individual reaction to dieting may be more important in the genesis of AN than dieting as such. (Fairburn, 1999) The number of people who have only a few or have relatively mild symptoms of AN greatly outnumber those who achieve syndrome status.

A diabetic with AN may deliberately underdose herself with insulin in order to reduce the metabolism of her food. Thyroid hormone may rarely be abused to reduce weight.

In restrictive AN, there is a severe restriction of calorie intake. In bulimic AN¹⁹²⁷, there is a severe restriction of food intake with episodes of binge eating (often nocturnal and in secret) ending with self-induced vomiting or the use of purgatives or diuretics. Early morning waking may occur in AN as a result of restlessness. Some cases go on eating binges, vomit¹⁹²⁸, or abuse purgatives. Problems include hypokalaemia, dehydration and, rarely, convulsions. Downy hair (lanugo), constipation, bradycardia¹⁹²⁹, orthostatic hypotension, peripheral cyanosis (acrocyanosis), bright orange skin (carotenoderma due to carotenaemia¹⁹³⁰), brittle hair and nails, anaemia¹⁹³¹, hypercholesterolaemia, a low blood pressure, hypothermia¹⁹³², hypokalaemic nephropathy, dependent oedema¹⁹³³, seizures¹⁹³⁴, leucopaenia with relative lymphocytosis, acute pancreatitis, gastric rupture, rectal prolapse¹⁹³⁵, muscle atrophy, neuropathies, a small heart with reduced heart muscle mass, QTc prolongation, ST-T wave abnormalities, cardiac arrhythmias and sudden death, and a fall in basal metabolic rate may all occur. The anorexic heart is unable to compensate for exercise. Elevated hepatic enzymes due to fatty degeneration of the liver may be found during starvation and refeeding. Cerebral ventricular enlargement, reduced gray and white matter, and cognitive dysfunction are described in AN.

A 'euthyroid sick syndrome'¹⁹³⁶ has been described in association with eating disorders. T3 and T4 are reduced but TSH is normal or only moderately reduced (one would expect an increase)¹⁹³⁷. No intervention is required¹⁹³⁸ because the findings normalise with recovery of the primary disorder. The stress of starvation is known to increase CSF endorphin levels, a possible explanation for the hypothesised addictiveness of weight loss.

Body image (perceived body size divided by actual body size: Wade *et al.*, 2003) is distorted: they think they are fatter than they really are. In fact, women with AN, bulimia nervosa or a combination of the two usually

¹⁹²² ICD-10 states that body weight is maintained at least 15% less than expected (lost or never gained).

¹⁹²³ Precedes obvious weight loss in 20% of cases; some authors feel that it is not an essential feature of the disorder. Patients on the contraceptive pill may still have vaginal bleeds.

¹⁹²⁴ Patients may acknowledge the need for admission after some time in hospital. (Guarda *et al.*, 2007)

¹⁹²⁵ Patients may prepare big meals for the family; patients may underfeed their own offspring.

¹⁹²⁶ Rats that are given only one meal per day and allowed to run on an activity wheel tend to reduce food intake and may run to the point of death. This has been 'explained' as a foraging response to food restriction and as a response to DA or endorphin release during starvation/exercise. Healthy male volunteers deprived of food become preoccupied with food, do not feel satiated after feeding, and will cook for others and enjoy watching them eat!

¹⁹²⁷ AN, binge-eating/purging type in DSM-IV.

¹⁹²⁸ People with peptic ulcer may induce vomiting to relieve pain.

¹⁹²⁹ Probably results from increased vagal tone. It is not benign (as in athletes) and is associated with reduced stroke volume.

¹⁹³⁰ E.g. on palms and soles.

¹⁹³¹ The classic normocytic hypochromic anaemia of starvation may be replaced by iron deficiency (microcytosis) in vegetarians.

¹⁹³² Hypothermia may mask infection.

¹⁹³³ Oedema is multifactorial in AN.

¹⁹³⁴ Due to electrolyte and fluid changes.

¹⁹³⁵ Usually found in long-standing cases with emaciation, emesis, and abuse of laxatives.

¹⁹³⁶ Or 'sick euthyroid syndrome'. In fact, any pattern of results can occur. This is a non-thyroidal disorder secondary to severe systemic upset (e.g. pneumonia, myocardial infarction). Peripheral conversion of T4 to T3 is decreased.

¹⁹³⁷ Some authors give a different description: low total T4, normal free T4, and low T3.

¹⁹³⁸ In fact, prescribed thyroid hormone could exacerbate metabolic and cardiac status in AN. Seek an independent cause of hypothyroidism if TSH is raised.

have body image distortion. AN has been described in the blind. Fear of fatness may not be universal in AN, e.g. in China.(Lee ea, 1993)

Bone loss in AN is significant, is related to the duration of illness, and improves to a variable degree with weight gain. However, a reduction in bone mass occurs even with brief illness and recovery may not be complete. Pathological fractures, including vertebral collapse, may occur. Stress fractures from excessive exercise (running and jumping) are another complication. Bone density does not correlate with basal oestrogen.

Eating Attitudes Test (EAT) was developed by Garner & Garfinkel in the late 1970s. A shortened, 26-item version is used to evaluate behaviours and attitudes found in anorexia nervosa (AN). A cut-off point is used to distinguish AN from normal controls. EAT has its limitations because classic eating disorders are uncommon – this reduces its positive predictive value (the proportion of true cases divided by the number scoring positive on the test) Using the EAT during the early 1990s, it was found Halpin & Fitzgerald (1992) 2.8% of Dublin adolescent males scored above the cut-off point, whereas between 6.8% of London schoolgirls scored positively and 13% of Dublin schoolgirls scored highly.

CT typically shows cortical atrophy following significant weight loss, reverting to normal with adequate nutrition, although some authors report persistent neurological (e.g. cerebellar) and neuroradiological (e.g. grey matter volume deficiencies) in AN. Functional imaging show increased metabolism in the caudate nucleus before weight restoration. A 1% reduction in global grey matter volume has been found on MRI and region specific grey matter loss in the anterior cingulate is directly related to clinical severity.(Mühlau ea, 2007) Impaired behavioural response shifting in AN¹⁹³⁹ may be associated with under activation of in the ventral anterior cingulate-striato-thalamic loop that subserves motivated behaviour, with AN patients showing mainly activation (on fMRI) of fronto-parietal networks that indicates effortful and supervisory cognitive control when performing a task.(Zastrow ea, 2009) Ventral striatal (reward system) activity on fMRI is higher in AN than in controls when processing underweight stimuli.(Fladung ea, 2010) There is mild lengthening of the QT interval in AN¹⁹⁴⁰, even in the absence of electrolyte imbalance, that may be due to autonomic imbalance secondary to starvation. Of unknown clinical significance, left ventricular mass is reduced. Clinical heart failure is a recognised complication of refeeding. (Reversible) mitral valve prolapse¹⁹⁴¹ is probably of similar prevalence to the general population. Sudden death has been reported which may be due to centrally or peripherally mediated autonomic imbalance, QT lengthening¹⁹⁴², or some other cause.(Cook & Chambers, 1995)

The family

Sheppard ea (1984) reviewed nine cases of male AN and wondered if the incidence of male AN might be on the increase. Male victims had a high incidence of affected relatives. They quote the literature as suggesting a figure of 25% for psychiatric illness among patients' relatives and stressed the amount of parental discord and role problems experienced by parents. OCD may be over represented among the mothers of patients with AN.(Halmi, 2003, p. 1007) The family discord could be covert, and the maternal affiliation may be very close with an absent or ineffectual father. Jacobs ea (2009) divided 'AN trios' (patient and two biological parents) into three classes: 33% consisted of mildly symptomatic patients and healthy mothers; 43% comprised probands who had strong drives for thinness, were unhappy with their bodies, and were neurotic, anxious (trait), and avoided harm and whose mothers had mild trait anxiety and perfectionism; and 24% where both mother and patient had eating disorders and had anxious, perfectionistic traits. Fathers did not differ markedly between the three groups. Minuchin ea (1978) described the family characteristics of AN cases as including enmeshment (overinvolvement with each other, unable to break away), rigidity (difficult to change behaviour patterns, even with increasing age), lack of conflict resolution (usually denied or avoided), overprotection, and involvement of the patient in family conflict regulation. Family dysfunction may be greater in the purging subgroup.(North ea, 1995) However, other workers (Blair ea, 1995) found no evidence for enmeshment, rigidity or weak boundaries between generations in AN families. Indeed, the results suggested that AN caused the family disturbance.

¹⁹³⁹ AN patients demonstrate difficulties with tasks that involve changing rules and give stereotyped or perseverative responses, i.e. they are inflexible.

¹⁹⁴⁰ The QT interval is prolonged in starvation and with electrolyte imbalance, a point to remember when prescribing medication.

¹⁹⁴¹ Listen for systolic click.

¹⁹⁴² Reported in people on a liquid protein diet. Prolonged QT found in AN even when serum electrolyte levels are normal.

As Morris and Twaddle (2007) point out, AN can be ‘found without apparent precipitants in otherwise well functioning families’.

Theories of causation in anorexia nervosa

‘Through the modern cult of youth, the body was becoming an object of worship through its initiation into a disappearing act’. (Porter, 2003, p. 243)

‘Anorexia has no single cause’. (Morris & Twaddle, 2007)

Socio-cultural: increasing recognition or incidence of AN; common in dance/ballet¹⁹⁴³ students (affecting as many as 25%), models (Treasure ea, 2008), and in well-to-do teenagers in developed countries; pressure on young people by advertisers/society to be thin¹⁹⁴⁴. (Becker ea, 2002; The McKnight Investigators, 2003) Gastrointestinal symptoms and picking at food during childhood correlates with anorectic behaviour in adolescence. (Marchi & Cohen, 1990) Pre-adolescent peer dietary characteristics influence eating behaviours and anxious children may be more susceptible to such influences. (Farrow ea, 2009) Excessive exercise (including competitive athletics) is common in the histories of AN patients; food restricted rats may run themselves to death on a wheel. (Konsman & Dantzer, 2002) Whilst disorders such as AN and type A behaviour have been described as Western culture-bound syndromes, AN and bulimia nervosa have been reported in non-whites.

Family pathology: ill child maintains family integrity by becoming a scapegoat for its problems; childhood mealtime disorganisation and maternal strong control and disharmony; (Cooper ea, 2004) but Blair ea (1995) - who compared normal families, families with a cystic fibrosis child and families with a daughter with AN - found little to distinguish such families; Stein ea (2006) found that 10-year-old children’s eating disturbance was associated with length of exposure to maternal eating disorder and mother-child mealtime conflict.

Genetic: tentative evidence: phenotype changeable. Possible link of restricted AN to chromosome 1p34. Chromosome 13 might be linked to drive for thinness, perhaps via the serotonin receptor gene (HTR2A). The BDNF gene may be important (Collier & Treasure, 2004), e.g. Ribases ea (2005), in a large European study¹⁹⁴⁵, found that the Met allele of a mis-sense variation in the BDNF gene was associated with AN. Serum BDNF levels may be low in AN and BN, but normal in recovered AN (Nakazato ea, 2009) and binge-eating disorder. (Monteleone ea, 2005)

Individual dynamics: child tries to escape from over-possessive (and perhaps older than average) parents through illness; child sexual abuse (CSA) may be important to later development of AN, bulimia nervosa, and obesity; a small number are premorbidly promiscuous or drug abusing; it has been said that there is no reduction in sexual interest in AN – whilst the present author’s cases have been quite varied in this regard it is probably true that the modern anorectic is more sexually active than was the case in the past; high levels of harm avoidance and lower self-directedness and cooperativeness might be trait characteristics in people prone to eating disorders (Klump ea, 2004) Psychoanalytic theories suggests a fear of oral impregnation; problems separating from mother (introject of interfering mother is ‘starved’ and own needs are projected into others who are cared for); and projective identification in relations

Developmental psychobiology: associated with Arthur Crisp; phobic avoidance of adolescent weight gain - is fat the main fear rather than food? Puberty arrested by slimming; mainly carbohydrates avoided; fear of fatness may be absent in some oriental cases of AN (Lee, 1994)

Hypothalamic disease: tumours may mimic AN (rare); most biochemical and physiological changes return normalise with weight gain - may include raised somatotrophin, increase in cortisol and loss of its normal diurnal variation, low T3, and decreased gonadotropins; the body seems unaffected by neuropeptide Y in AN; some authors point out that 20% of cases stop menstruating before losing weight and that the rate of cortisol is increased in AN but reduced in starvation, suggesting a possible primary endocrine disorder

Other organic: dysmorphic delusions in temporal lobe epilepsy (rare); pro-inflammatory cytokines, whilst having important effects on food intake and weight in conditions like cancer and AIDS, probably have little

¹⁹⁴³ Being in a dance class, having higher concern about body shape, and lower family support is associated with having an eating disorder in Taiwan. (Tseng ea, 2007)

¹⁹⁴⁴ However, pressure on wealthy people to achieve a slim figure was ‘well-established’ by the 1920s. (Brunton, 2004, p. 368) Nevertheless, the advent of Western TV to Fiji may had been responsible for an increase in eating disorder among adolescent females. (Becker ea, 2002)

¹⁹⁴⁵ N = 1,500 patients.

role in AN; right frontal lesions may closely mimic AN (Uher ea, 2002); various perinatal problems (Favaro ea, 2006, 2010) such as 'dysmaturity'

Abnormal serotonin transmission – blunted prolactin response to d-fenfluramine, persistent altered serotonergic function and anxiety after recovery from AN (Bailer ea, 2005)

Affective disorder: primary or secondary? Mangweth ea, (2003) in a study of relatively small sample size, found that the familial aggregation of eating disorders (AN, BN, and binge-eating disorder) with mood disorders was significant and of the same magnitude as the aggregation of mood disorders alone.

Anorexia – true loss of appetite only occurs in severe, late stages

Differential diagnosis

This includes Simmond's disease, TB, malignancy, alcohol and drug abuse, affective disorders, paranoid psychoses, political hunger strikes, food fads, malabsorption states, and other causes of primary and secondary amenorrhoea.

Malignancy, chronic organ failure, GIT disorders, endocrine disorders, chromosomal abnormalities, and deprivation/abuse should be outruled in prepubertal cases. Women who are taking contraceptive pills or hormone replacement therapy (HRT) may have vaginal bleeds, but this does not outrule a diagnosis of AN.

Cognition

People with eating disorders appear to have problems with global processing of information. (Lopez ea, 2008) In *selective abstraction* an isolated detail is used as to make an important conclusion. An example of *overgeneralization* includes the belief that the slightest use of carbohydrates would cause obesity.

Magnification is the overestimation of the significance of undesirable events. *All-or-nothing reasoning* includes the idea that the slightest weight gain will snowball toward obesity. An example of *excessive self-reference* would be 'I feel embarrassed when other people watch me eat'. In *magical thinking* a sweet is considered to be automatically and instantly converted to fat.

*Set-shifting*¹⁹⁴⁶ problems occur in eating disorders. (Roberts ea, 2007)

Management

Some cases do well with minimal intervention whilst others may require huge investments of time and may cause the therapist to despair. (Russell, 2004) It is hardly surprising that out-patient failures do poorly when admitted. (Gowers ea, 2007) Management comes down to putting on (post-voiding and gowned) weight¹⁹⁴⁷ and psychotherapy, individual and family. Expressed emotion in the family, if excessive, should be the subject of intervention. Day programmes for both AN and bulimia nervosa have become more popular than previously. The reasons why patients are admitted more or less readily in different jurisdictions may be more to do with financial and litigation considerations than any scientifico-medical thinking.

Psychotherapy for AN

Not recommended: Randomised trial of **CBT and interpersonal therapy** (McIntosh ea, 2005): neither active treatment was better than non-specific clinical management

Recommended: Longterm **Motivational enhancement therapy/interviewing**¹⁹⁴⁸, a non-psychodynamic approach dealing with manifest thoughts and actions, is used to avoid unhelpful patient responses (e.g. anger or deception)

Recommended: Family therapy to educate the family, avoid excess permissiveness (secondary gain), and to provide support (Eisler ea, 2000)

Monitor potassium¹⁹⁴⁹, magnesium, calcium and phosphate during early treatment. Rapid re-feeding and weight gain may lead to serious consequences (see box).

Re-feeding syndrome

¹⁹⁴⁶ Set-shifting, an important executive function, is the ability to move back and forth between many tasks, operations, or mental sets. It may show as inflexible thinking (concrete, rigid, stimulus-bound) or responding (perseverative or stereotyped).

¹⁹⁴⁷ Beware of patients who place weights in their pockets or who drink large amounts of water. Also, if purging is suddenly stopped rebound oedema may increase a patient's weight.

¹⁹⁴⁸ Derived from work with substance misuse – reframe resistance to change as ambivalence about change.

¹⁹⁴⁹ Hypokalaemia is common in people who vomit. Potassium supplements may be required.

Depleted body reserves of substances such as potassium and phosphates
 Stimulation of metabolism by re-feeding increases demands for such intracellular substances
 Body must draw on plasma for these chemicals
 Can cause gastric bloating, dyspnoea, weakness, oedema, hypophosphataemia, seizures, delirium, coma, haemolytic anaemia, and rarely congestive cardiac failure
 Thiamine deficiency may lead to delirium, especially in the second week of re-feeding

To achieve the essential weight a behavioural regimen¹⁹⁵⁰ is used, privileges are granted only on reaching a certain body weight. However, operant approaches have been criticised as being coercive and are now less popular. Personal belongings are not withheld. Patients may secrete food on their person or elsewhere, or carry weights to weigh down the scales. Good nursing supervision is essential¹⁹⁵¹. Drugs (trimipramine, chlorpromazine¹⁹⁵², cyproheptadine [Periactin¹⁹⁵³], and insulin) were commonly used in the past but were generally ineffective. An exception is the use of antidepressants (e.g. fluoxetine, reboxetine, venlafaxine) for comorbid depression.¹⁹⁵⁴ SSRIs do not help the low-weight state, possibly because of a lack of serotonin to prevent the uptake of. (Brewerton, 2002) Fluoxetine may assist with weight maintenance, but citalopram has led to weight loss. (APA, 2002, pp. 733-4) Olanzapine has been used with some success to improve weight gain during refeeding. (see Connan, 2002, p. 1141) It may also have some effect on distorted beliefs, anxiety, and agitation. (Hodes ea, 2008, p. 846; Bissada ea, 2008) Bupropion (Zyban) is contraindicated by the manufacturers in AN. As a general rule, drug treatments are best delayed until following weight restoration or at least until hepatic function and electrolyte balance are normalised. A disturbing development is the presence of internet ('pro-ana') sites that promote anorexic eating practices and divert people from seeking professional help.

Prognosis

Periods may not return for months after weight restoration. According to Patton (1989) about 1 in 30 AN patients will die, and half will recover fully after 6 years. Robert Palmer (2003) of Leicester stated that, whilst AN causes much morbidity, most cases recover eventually. The predictors for death were lowest reported weight and repeated hospital admissions. Half of those who died had killed themselves through overdose. Suicide seems to be more common among bingeing/purging patients than among restricting types. Franko ea (2004) found that severity of depressive symptoms and drug use predicted suicide attempts in AN. Predictors of poor outcome were lowest weight, length of illness, older age at onset, and disturbed family relationships. Chronic, low weight cases may show CT evidence of irreversible ventricular enlargement and partially reversible sulcal enlargement¹⁹⁵⁵. Patients may be arrested for stealing food, clothes, laxatives¹⁹⁵⁶, or other items.

Unlike most research, certain population-based studies (Wentz ea, 2001; Korndorfer ea, 2003) have reported no excess mortality in AN – perhaps explained by inclusion of milder cases, population characteristics, or reduced deaths from obesity-related cardiovascular diseases.

Finnish female twin study (Keski-Rahkonen ea, 2007)
 Lifetime prevalence of DSM-IV AN was 2.2% (higher than usual)
 Half the cases were not detected by health care services
 Incidence in females 15-19 years = 270/100,000 person years
 5-year recovery rate = 66.8%
 Outcome no different whether detected or not!

¹⁹⁵⁰ This is now less strict than was the case in the past. Less strict approaches may be just as effective. Vitamin and mineral supplements are often prescribed. If oral feeding fails the nasogastric feeding may be necessary; feeding via gastrostomy or jejunostomy have been used rarely; and total parenteral nutrition tends to be avoided because of attendant complications.

¹⁹⁵¹ The nurse helps the patient to see that eating need not be equated with loss of control over her body weight, to maintain clear targets, and to prevent vomiting/purging.

¹⁹⁵² Chlorpromazine is sometimes given to reduce mealtime nausea in purging anorexics.

¹⁹⁵³ An antihistamine used to treat allergic symptoms; has been used to stimulate appetite in the medically ill; can cause sedation and dry mouth/nose/airways.

¹⁹⁵⁴ It should be noted that depression often improves as weight is restored. Weight loss through dieting lowers tryptophan availability.

¹⁹⁵⁵ I.e. reversing when weight is put on.

¹⁹⁵⁶ The sweetener sorbitol can cause an osmotic laxative effect and weight loss. It is present in many foods, including chewing gum. It, like mannitol and xylitol, is a polyalcohol sugar. (Bauditz ea, 2008)

By 5 years the AN cases were just like their co-twins in every way (fully recovered)

Babies of AN women tend to have a low birth weight.(Micali ea, 2007)

Male AN: some issues

The reasons why AN is less common in males can only be guessed at. Possibilities might relate to a later age at puberty, testosterone, and a society that advocates fitness rather than thinness.(Buckley ea, 1991) Instead of amenorrhoea, male cases have loss of libido and impotence

Prepubertal AN

This is uncommon¹⁹⁵⁷. In a large series of cases the males make up a third, which is markedly different from the male to female ratio found in older age groups. They may have failure to gain weight rather than loss of weight, and hormonal changes are not as obvious. Some cases may fail to grow in stature. Girls do not develop breasts and have primary amenorrhoea. Boys have juvenile genitalia. If recovery occurs, puberty will often be completed normally but the onset of menses will be delayed. Depression is common. Admission may be required for joint medical and psychiatric assessment. Growth may be stunted and breast development may be severely affected. The menarche may be delayed. Early feeding difficulties may be elicited, and there may be a history of feeding problems (such as fads) in the family. Adverse life events appear to precipitate AN more commonly in prepubertal cases. They may have a history of early behavioural difficulties with poor peer relationships. There may, in some cases, be a positive family history of AN (found in 7-10% of first-degree relatives in AN of older onset). There is an increased history of family psychiatric disorder. There is also a high level of family disturbance with an excess of overinvolvement and a disturbance in parent-child relationships, and evidence of problems in intrafamilial communication. These youthful cases are treated as inpatients. The ward milieu should provide a safe environment with age-appropriate firm handling. Drugs are only used for associated depression, and amitriptyline has been recommended, although SSRIs appear safer. Family therapy is important to improve problem-solving skills. The parents may be helped to form a strong, effective alliance, and so to take control of their child's food intake. The prognosis is complex, and more follow-up studies are needed. Certain factors, such as depressive features and one-parent families, are associated with a poor outlook.

AN in the elderly

AN can occur in older people, affecting women more often than men. Amenorrhoea, of course, cannot be used diagnostically. Some cases seem to be precipitated by stress, such as bereavement. About two-thirds improve with treatment.(Nicholson & Balance, 1998) It is important not to misdiagnose another disorder, psychotic depression, as AN in this age group.

Bulimia nervosa (BN)¹⁹⁵⁸

Epidemiology

Some authors suggest that BN is a product of the late 20th century, pointing to its apparent absence in older cohorts. Drewnowski ea,(1988) in a prospective study, found an incidence of 2.1% per 6 months among female freshman students, or 4.2 new cases per 100 women per year. Emergent cases were offset by partial remission. Therefore the prevalence rates remained stable between their autumn and spring surveys. Hsu ea (1987) reported that BN affected 2-19% of young women in England and in the US.

Aetiology

Kassett ea (1989) reported that the close relatives of BN patients are found to have an excess of major affective disorders, eating disorders, and alcoholism when compared with control subjects. They surmised that major mood disorders and BN might be caused by a common diathesis. Others see anxiety and depression as secondary phenomena, and while BN patients may have the same total scores as primary depressives on depression rating scales the profiles may be very different (i.e. the items scored differ between the two groups).(Cooper & Fairburn, 1986)

¹⁹⁵⁷ There is evidence that puberty influences expression of genes for disordered eating.(Klump ea, 2007)

¹⁹⁵⁸ Russell (1979) described BN (bulimia = 'ox hunger') as a variant of AN ('A sister spawned from anorexia nervosa', to quote Gerard Russell at a talk given to the Royal Academy of Medicine in Ireland, Dublin, 09.03.1999). His diagnostic criteria are no loss of insight, bouts of subjectively excessive overeating, dieting, vomiting, purging, abuse of diuretics or anorectics, and awareness of and upset by slight increases in weight and/or shape. Famous cases are Princess Diana and Jane Fonda (see her *My Life So Far*).

Stein and Fairburn (1989) reported that as children their cases were ignored or smacked, had problems with breast-feeding, were too heavy or too light in childhood, and their parents may have been over-concerned about the child's size. Marchi and Cohen (1990) found mealtime problem behaviours and early pica to be associated with BN during adolescence. Waller (1991) found that bulimics reported more CSA in their histories than did anorexics and suggested that CSA was not a cause of eating disorder per se but perhaps might determine its final form. Pope and Hudson (1992) found no support for a causative role for CSA in BN. Other reports of the connection between CSA and BN are summarised in the table.

Kendler ea (1991), using DSM-III-R criteria, looked at female twins from a population-based register. Risk factors for BN were birth after 1960, low paternal care, widely fluctuating weight, dieting, frequent exercise, slim body image, low self esteem, external locus of control, and high neuroticism. Concordance for narrowly defined BN for MZ twins was 22.9% and for DZ twins it was 8.7%. Sullivan ea (1998) suggested that bingeing and vomiting in their population-based sample of female twins (n=1897) were due to the influence (mainly) of multiple genes and (less so) individual-specific environmental influences. BN with self-induced vomiting and obesity may be linked to chromosome 10p.(Bulik ea, 2003)
BN patients may have a blunted ghrelin¹⁹⁵⁹ response to food intake, normals showing a drastic decrease in circulating ghrelin under such circumstances.(Monteleone ea, 2003)

Eating disorders and child sexual abuse (CSA, in temporal order)

<i>Findings</i>	<i>Comments</i>
CSA associated with more bingeing and, to lesser extent, with vomiting	Females, Britain
Borderline personality disorder may partly explain the alleged connection	
CSA not a factor in BN	Women in US, Brazil, Australia
CSA only one type of abuse experienced	Women in California
CSA not essential; general childhood abuse common	Austrian female university students
CSA vulnerability factor for psychiatric disorder in general but not EDs in particular	Normal controls and depressives
44% of BN cases reported CSA but these had many other difficulties*	
A real, non-specific aetiological factor	Russell, G, Dublin, March 9, 1999
There is no specific sexual abuse syndrome	Adult female twins
Recall of parental mental health problems and early unwanted sexual experience assoc. with lifetime eating problems, laxative use and vomiting in pregnancy and marked concern over shape/weight in pregnancy	

Eating disorder = ED; bulimia nervosa = BN

*More depression, earlier onset of BN, worse overall functioning, alcohol and substance dependence, conduct disorder, etc.

Patients with BN may not engage frontostriatal circuits (subserving self-control) appropriately (Marsh ea, 2009). CSF 5-HIAA levels are low in BN.(e.g. Jimerson ea, 1997)

Diagnosis & clinical features

A diagnosis of AN takes precedence over a diagnosis of BN. The majority of AN sufferers are restrictive, but the minority (bulimic AN) overlap with BN.

The *Bulimic Investigation Test Edinburgh* (BITE) is a brief questionnaire used for the detection and description of binge eating. The scale has measures of both symptoms and severity.(Henderson & Freeman, 1987)

Individual components of the syndrome are common. Patients seek help either if the condition is severe (they spend quite a lot of money on food) or if there is associated severe anxiety or depression. Nearly all cases are female, but there is a certain amount of evidence that more men with eating disorders may have BN than AN and that there may be an excess of homosexuality or bisexuality among these males.(Carlat ea, 1997) One-quarter are married. They are somewhat older than AN cases. About 50% of AN cases have bulimic episodes.

BN patients have bouts of secretive overeating which they feel are excessive and beyond their control. Disgust is common. They may weigh themselves several times a day. The feminine curves of the lower

¹⁹⁵⁹ **Ghrelin** is 28-amino-acetylated peptide. It is produced in the gastric fundus by oxyntic cells.

torso occupy much of their attention. They may socially isolate themselves if they feel that they are gaining weight. They view themselves as expert dieticians, may pride themselves on their cooking prowess, and may work in the catering trade. A few practice regurgitation and rumination. They may vomit up their food later, spit it out there and then, or drink large amounts of fluids to assist vomiting. Absorption of food is enough to keep them around normal weight. Jogging and keep-fit classes are common pastimes. Stealing food from shops is not uncommon in BN.

Obsessive-compulsive symptoms are common during bulimia and during recovery. It is possible that these are traits rather than state symptoms.

Oligomenorrhoea, amenorrhoea (perhaps in one-third of cases: Hodes *et al.*, 2008, p. 847) and irregular menses may occur, even in the absence of low weight.

BN has been divided into purging (self-induced vomiting or laxative abuse present) and non-purging (self-induced vomiting or laxative abuse absent) types.

PET studies suggest that left anterolateral prefrontal cortex hypometabolism may vary with the level of depressive symptoms in BN.

Comorbidity

Comorbidity (e.g. depression, personality disorder, or substance abuse) is present more often than not. (Yates *et al.*, 1989) Van Hanswijck de Jonge *et al.* (2003) found that binge eating in eating disorders is more strongly associated with personality disorder than is the absence of binge eating in such conditions. Thompson-Brenner and Westen (2005) found that most patients with bulimic symptoms matched one of three personality subtypes (high-functioning/perfectionistic, emotionally dysregulated/undercontrolled and emotionally constricted/overcontrolled) and that those who were more dysregulated or constricted take longer to treat and do less well. Kendler *et al.* (1991), referred to above, found significant comorbidity with AN, alcohol abuse, panic disorder, GAD, phobia, and major depression. Overdosing is not uncommon. (Lacey, 1993) Franko *et al.* (2004) found that laxative use and a history of substance use predicted suicide attempts in their prospective study. Perhaps a third of BN cases have a history of AN, and a minority have both syndromes simultaneously.

Complications

There can be erosion of dental enamel, buccal tears, enlarged parotids (*chipmunk facies*)¹⁹⁶⁰, enlarged submandibular glands, downy hair growth (e.g. upper lip and forearms), tetanic spasm, and scarring/calluses over the first metacarpo-phalangeal joint due to the gnawing effect of the upper incisor teeth during self-induced emesis (Russell's sign). Stopping diuretics may lead to rebound oedema thus perpetuating their use. Excess ipecac may cause cardiac problems: cardiac failure due to cardiomyopathy in these cases is very often fatal; symptoms such as chest pain, dyspnoea, generalised muscle weakness, hypotension, tachycardia, raised serum aldolase concentration, and ECG changes should suggest the likelihood of ipecac poisoning. Hypokalaemia is sometimes avoided by potassium supplementation. Many cases of BN have elevated serum bicarbonate levels, but a few have reduced levels (metabolic acidosis, especially if abusing laxatives). Fractures may occur due to low oestrogen levels and consequent osteopenia.

There may be impulsiveness, alcohol and drug abuse, promiscuity, stealing for food, irritability, anxiety, depression, fractures, hypokalaemia, convulsions, cardiac arrhythmias, finger clubbing¹⁹⁶¹, fatty stools, hoarseness, damage to dentition, acute gastric dilatation, medication loss from purging¹⁹⁶², and obesity from eating excessively.

BN patients often have anovulation and menstrual problems despite a normal weight. This might be due to gross fluctuations in carbohydrate intake, disturbances of fluid and electrolyte balance caused by self-induced vomiting and laxative abuse, or by vomiting leading to excessive dopamine activity centrally. BN may improve during pregnancy only to return during the puerperium¹⁹⁶³. There may be an increased risk among those with active AN or BN of Caesarean section and postpartum depression. (Franko *et al.*, 2001) A history of miscarriages is relatively common among women with BN. (Micali *et al.*, 2007) The risk of suicide

¹⁹⁶⁰ With increased serum amylase levels if bingeing and vomiting. Salivary isoenzyme of amylase will be raised with parotid enlargement.

¹⁹⁶¹ Purgative abuse is an uncommon cause of clubbing.

¹⁹⁶² Giving medication at bedtime may help.

¹⁹⁶³ See Ward (2008) for discussion of eating disorders and pregnancy: treat before pregnancy, provide nutritional education, refer early if disorder is active, observe for postnatal depression or worsening of disorder, support breastfeeding, and monitor baby.

is increased in BN. In fact, the mortality rate has been said to be the highest of any (presumably 'functional') psychiatric disorder.

Management

Cognitive-behavioural therapy (CBT)¹⁹⁶⁴ is offered as an outpatient over a number of months (average 20 sessions over 6 months). The beneficial effects of CBT seem to outlast active treatment, an attribute that may be true for drugs. Personality disorder alone may not reduce the effectiveness of CBT, but comorbidity with depression and low weight may do so. Emphasis is placed on regular eating habits. Dietary diary keeping is encouraged. Education about the eating disorder is furnished, as well as the normal body weight changes to be expected over time. Other problem-solving strategies are explored. An attempt is made to change fixed, maladaptive ways of looking at things. Interpersonal psychotherapy has produced good results, at least as good as CBT in some studies. Serum amylase estimations may be used to monitor vomiting behaviour.

Antidepressants of a number of classes¹⁹⁶⁵ have been reported as alleviating the symptoms of BN. SSRIs,¹⁹⁶⁶ particularly fluoxetine, may facilitate weight loss¹⁹⁶⁷. Since desipramine has been shown to be effective, it has been suggested that antidepressants may actually work by reducing hunger. 5-HT₃ antagonists, such as ondansetron, may have anti-bulimic effects.(Faris ea, 2000) D-fenfluramine, a 5-HT agonist, whilst it was useful in overweight patients was ineffective in BN. Topiramate, the dose of which should be increased gradually, reduces binge eating and purging in BN and can cause paraesthesiae, weight loss, and interfere with cognition. Bupropion (Zyban) is contraindicated in bulimia nervosa because of an associated high incidence of seizures. Also, trazodone has been associated with delirium in this patient group.

The combination of CBT and antidepressants may be more effective than either alone, but the literature is conflicting.

Prognosis

According to Keski-Rahkonen ea (2009) BN is often missed by clinicians, the condition is relatively chronic, and recovery is gradual, and, even when bingeing and purging is abandoned, psychological symptoms are common. Poor prognosis has been reported in association with high BDI scores on admission¹⁹⁶⁸ and (even subthreshold) vomiting. In general, a poor prognosis is associated with psychiatric comorbidity, mixed AN-BN, severe symptoms, and a lack of social supports. Good prognosis has associated with younger age at onset, higher socioeconomic status, and a family history of alcohol abuse. A number of authors (e.g. Kaye ea, 2000) have reported either relapse or exacerbation of BN following acute depletion of L-tryptophan.

Other eating disorder

The DSM-IV approach in terms of how much a case must binge or vomit strongly underestimates the frequency of such behaviours in the population at large. Clinicians encounter people who lack one or more features of AN or BN, i.e. partial syndromes. They also see cases that are not severe enough to warrant a diagnosis of AN or BN, i.e. subthreshold disorders. Anxious people who vomit those people who stop eating for attention-seeking reasons (personality disorder, political hunger strike) are not suffering from a formal eating disorder.

People who recurrently binge but have no other features of BN may be said to have 'binge-eating disorder',¹⁹⁶⁹ a syndrome that is reminiscent of what is commonly called compulsive overeating. (Cf. box)

Binge eating disorder

Two percent of women have this 'stable'¹⁹⁷⁰ (Pope ea, 2006) disorder and the M:F ratio is 2:3 making it the eating disorder with the highest rate for males. Like AN and BN, binge-eating disorder may be uncommon

¹⁹⁶⁴ **Phases of CBT in bulimia nervosa:** (1) Careful history and self-monitoring: food intake, binge eating, purging. (2) Slow shaping of at least 3 meals/day to shorten the long intervals between eating episodes typical of BN and to lessen dietary restraint. (3) Tackle cognitive distortions regarding caloric intake and body shape and weight. (4) Relapse prevention, e.g. coping with high-risk situations.

¹⁹⁶⁵ Because MAOIs have been associated with fatalities in BN as a result of non-adherence to dietary restrictions they should be avoided in this population.

¹⁹⁶⁶ Zimeldine (Zelmid), a 5-HT re-uptake inhibitor, was shown to be helpful but it was withdrawn because of an association with the Guillain-Barré syndrome. The newer SSRIs have stepped into the place vacated by zimeldine.

¹⁹⁶⁷ Paroxetine may cause weight gain.

¹⁹⁶⁸ But other workers found depression to be a non-significant prognosticator.

¹⁹⁶⁹ This was first described by Stunkard.(1959)

in black women.(Striegel-Moore ea, 2003) Childhood obesity and familial eating problems are risk factors for binge-eating disorder.(Striegel-Moore ea, 2005)There is consumption of large quantities of food in a short period of time, a sense of loss of control, followed by guilt and distress but no compensatory behaviours such as vomiting or laxative abuse. This pattern should occur at least two days per week for six months. Most, but not all, cases are obese. Binges may be driven by emotion more than hunger since the salivary response to food exposure is diminished.(Karhunen ea, 1997) CBT and interpersonal psychotherapy appear to be helpful (Shafran ea, 2008, p. 633; Wilson ea, 2010) and fluoxetine performed more poorly than CBT in one study.(Grilo ea, 2005) Guided self-help on CBT appear to be effective.(Wilson ea, 2010) Sertraline has been shown to be helpful and to be well tolerated. D-fenfluramine reduces the rate of bingeing at first but loses efficacy thereafter. Sibutramine¹⁹⁷¹ (Q.V.) has been effective and well tolerated in a study from Brazil.(Appolinario ea, 2003)

Purging disorder

Proposed subtype of eating disorder not otherwise specified.(Keel ea, 2005) It resembles BN but lacks full blown binge-eating episodes.

Night-eating syndrome

Prior to the description of binge-eating disorder, Stunkard ea (1955) described a 'night-eating syndrome', also known as nocturnal eating or drinking syndrome or 'sleep-related eating disorder'. The syndrome may affect 1.1-1.5% of the general population and many more people in weight reduction programs or awaiting bariatric surgery. Episodes occur before or at any time during the sleep period. Patients may be groggy during an episode and feel ashamed of what they have done. They may reduce their diurnal food intake in order to compensate for nocturnal eating or feeding behaviour may be normal by day. Some authors draw a distinction between night-eating syndrome (full consciousness, eating excessively before retiring or during awakenings) and sleep-related eating disorder (arising from non-REM sleep) on the basis of the level of awareness but they probably represent a continuum. Various drugs can precipitate the syndrome (anticholinergics, lithium, triazolam, zolpidem) as can drug withdrawal (including tobacco and alcohol) and dieting, stress, and narcolepsy. The classic case is an obese woman who eats or drinks excessively during the night ('evening hyperphagia' or taking in at least one-quarter of daily calories after supper). The condition may lead to obesity.(Stunkard ea, 2008) Chronic insomnia occurs (awakenings with ingestions at least 3 times/week). SPECT shows a significant increase in 5-HT transporters in the midbrain. SSRIs are the treatment of choice.(O'Reardon ea, 2006; Stunkard & O'Reardon, 2009)

Psychogenic vomiting

It has been suggested that there is a disorder called 'psychogenic vomiting' (Anonymous, 1992) in which there is chronic and episodic vomiting following meals and not accompanied by nausea. It is said to be less common than BN (self-induced following episodes of uncontrolled overeating), to be more common in females, and usually presenting in early or middle adult life. Treatment suggestions include psychotherapy and behaviour therapy.

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¹⁹⁷⁰ Shafran ea (2008, p. 633) suggest that this condition has a high spontaneous remission rate ('at least in the short term') and a 'relatively high response to placebo'.

¹⁹⁷¹ Specific reuptake inhibition of noradrenaline and 5-HT; causes dry mouth and constipation, and rebound weight gain may follow cessation of treatment.

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16

Abuse of women, children and elders

Brian O'Shea

Many different people are at increased risk of suffering from abuse, e.g. the institutionalised, minority populations and those with intellectual disability. The latter are living longer than before and, because of the loss of loved ones, may be exploited, neglected or abused in some other way.(Turk & Brown, 1993) Factitious disorder by proxy, a disorder with a high lethality (Sheridan, 2003), is discussed elsewhere.

Violence against women

Most violence against women¹⁹⁷² is global, widespread, ongoing, under-reported, and is associated with poor physical and mental health.(Kumar ea, 2005; Clark & Wyshak, 2005; Ferris, 2007; Ellsberg ea, 2008) Perpetrators vary from spouses to bosses.(Watts & Zimmerman, 2002) Like many trauma survivors in general, survivors of domestic violence with PTSD have dysregulated HPA axes.(Griffin ea, 2005) According to Scott (1974), wife battering is often part of a wider 'battering family' and is associated with immaturity, jealousy, substance use and dependence, dependency, fear of loneliness, ignorance about more mature relationship patterns, personality disorder (particularly dependent and aggressive types), psychiatric illness in general, and, possibly rarely, sadomasochism. Gender inequality, be this in the social or muscular sense, seems an obvious factor.(Jewkes, 2002) According to Buist ea (2007, p. 436) some women remain in abusive relationships because they were abused as children and had inadequate parenting resulting in a poor self-image. However, women who leave an abusive relationship are at increased risk of lethal violence and the perpetrator often controls the available finances.(Beck, 2008, p. 1125) A woman may also stay in such a relationship in order to protect her children or because she has been manipulated into feeling responsible for or deserving of abuse.(Beck, 2008, p. 1130) Also, illegal aliens may fear deportation. Kyriacou ea (1999) lists the characteristics of the battering male partner as abusing alcohol or drugs, unemployed or intermittently working, less than high-school educated, and a former or estranged husband/boyfriend of the victim. Drug abuse in the victim may also be a factor.(Grisso ea, 1999) In one sample of American women,(Martin ea, 2001) 6.9% were abused before pregnancy, 6.1% during pregnancy, and 3.2% during the first few months postpartum. Violence during pregnancy¹⁹⁷³ seems to be more common when the pregnancy is unwanted or mistimed,(Gazmararian ea, 1995) and victims are not likely to inform medical staff (O'Donnell ea, 2000) or to be asked about it.(Bradley ea, 2002; Richardson ea, 2002) The antenatal clinic provides an opportunity to make enquiries about domestic violence.(McDonnell ea, 2006) Hegarty ea (2008) suggest that where intimate partner violence is suspected that all family members should be asked about any abuse in the family, that the safety of all family members should be checked on, that a safety plan may be necessary, that the response should be non-judgmental, on-going support should be offered, and that women and children should be referred to advocacy and therapeutic programmes, but that couple counselling is not to be offered outside specialist agencies. Do not raise the question of intimate partner violence with a perpetrator without the victim's permission.

¹⁹⁷² Such violence takes many forms, varying from forced prostitution and trafficking through domestic sexual abuse to wartime rape and female infanticide or selective abortion of girls.(Plafker, 2002; Fikree & Pasha, 2004; Sheth, 2006; Jha ea, 2006) About 1.2 million children are traded as commodities every year. The BMA points out that domestic abuse can be physical, sexual, psychological, and financial.(www.bma.org.uk) Sexual exploitation of children by UN peacekeepers and non-governmental (NGO) workers came to light in 2008; the UN is relatively powerless in such situations and member states must take responsibility.(Anonymous, 2008c) Rates of violence among same-sex couples are probably on a par with those in heterosexual households.(Beck, 2008, p. 1125)

¹⁹⁷³ The pregnant woman is likely to be beaten on the abdomen, the non-pregnant woman is more often struck in the face.(Stewart & Robinson, 1995) Spousal violence in Africa was shown to be associated with increased likelihood of single and repeated fetal loss, largely due to violence.(Alio ea, 2009)

Children should be educated about abuse in order to prevent the development of ingrained negative attitudes toward women and the 'normalisation' of violence and intimate partner violence should be viewed as unacceptable and morally abhorrent by the community. (Anonymous, 2009a)

Honour killings usually refers to the murder of a female relative by a man who does so because he believes the woman has shamed the family, e.g. by infidelity. In Pakistan in 2007 women were the victims of 636 honour killings, 731 rapes, and 736 kidnappings. (Anonymous, 2008; see Dobson, 2009) In one study of homicide in the Middle East honour killing was common and mostly committed by a brother. (Kulwicki, 2002) It would be a mistake to believe that such acts were confined to Muslims. The core problem appears to be the inferior or even slave status given to women. (Lafta, 2008)

Physical violence directed against male partners by women is not uncommon but tends to be less violent than *vice versa*. It is generally in self defence.

Child sexual abuse (CSA)¹⁹⁷⁴

Child sexual abuse (CSA) is not new (O'Shea, 2001a,b,c, 2009) but has received much greater coverage by the media than heretofore, largely as a result of 'revelations' of abuse by persons in positions of authority¹⁹⁷⁵. It is an international problem. (Reza ea, 2009) Historically, the first modern work on child sexual abuse (CSA) was that of Tardieu¹⁹⁷⁶ in 1857, although his writings were largely ignored. In 1883, Brouardel¹⁹⁷⁷ dismissed CSA as the result of genital hallucinations or a tactic to gain attention. Freud was convinced of the role of CSA in neurosis early in his career only to change his mind later when he stated that such reminiscences were imaginary. By that time he had alienated a number of his supporters because of his emphasis on the role of sex in the origins of neurosis.

Child maltreatment, including, CSA is a violation of children's human rights (Reading ea, 2009), be it at the level of the individual, institution, or wider in society. CSA is a sexual act imposed on a child, irrespective of its emotional, maturational, and cognitive development. Children cannot legally give informed consent for sex. Under Irish law, child abuse includes physical neglect¹⁹⁷⁸, CSA¹⁹⁷⁹, and adverse

¹⁹⁷⁴ This is discussed here because of its topicality and importance in practice with adult patients. Apart from CSA there may be neglect (extremely common: the child is not protected or cared for) or emotional abuse (persistent and severe rejection or maltreatment that jeopardises emotional/behavioural health, e.g. rejection, harassment, criticism, ridicule, humiliation, and threats; the child is usually neglected and emotionally abused). **Emotional abuse** may involve encouragement to develop inappropriate behaviour (ranging from drug abuse to sexual acts), preventing wider societal experience, non-inclusion in family activities, not providing emotional warmth, humiliation, intimidation, and exposure to violence, and generally poor parenting (unreliable, inconsistent, unpredictably changing rules, etc). The **National Counselling Service** (helpline 1800-234-111; www.hse-ncs.ie) provides free confidential professional counselling and psychotherapy for adults who were abused or neglected in childhood; the counsellor/therapist has a reporting duty if he/she 'has a reasonable concern that harm may be done to yourself, another, or where a child may be at current risk of abuse or neglect'. Delays of 'a number of months' before therapy are possible.

In 2009, the *Irish Medical Council* (medicalcouncil.ie) stated that child abuse/neglect must be reported to the appropriate authorities and/or statutory agency without delay and parents/guardians should be so informed unless doing so places the child in danger. If an adult discloses a history of childhood abuse the doctor must assess current risk to others and if someone is likely to be at risk the clinician should report the revelation, preferably with the patient's consent.

Of 3 million reports of alleged incidents of child maltreatment to US protective agencies in 2005 one in three were substantiated. 60%, 20%, 10%, and 5% of substantiated cases involve neglect, physical abuse, sexual, and emotional abuse, the remainder being unspecified; about 1,500 American children die each year from maltreatment. (US Department of Health and Human Services, Administration on Children, Youth and Families, 2007)

A systematic review of 23 prospective studies based on 16 cohorts (Weich ea, 2009) found that abusive parenting predicted depression, anxiety and PTSD and that maternal early emotional unavailability predicted attempted suicide in adolescents.

¹⁹⁷⁵ See the *Ryan and Murphy Reports* in Ireland of 2009 which looked at institutional and Dublin Archdiocese child abuse respectively. This author was well aware of such events at the rumour level when a schoolboy, but it was not something one confided to adults at the time. (O'Shea, 2009) Neither did one complain much of the corporal punishment handed out in school, although the latter would readily meet modern criteria for brutality. These Irish scandals are not unique and such abuse of power and cover up by society in general have an international dimension. (Anonymous, 2009b) Pope Benedict XVI sent a written apology to Irish victims of clerical sex abuse in March 2010. He called for a strengthening of child protection policies by the priesthood.

¹⁹⁷⁶ Auguste Ambroise Tardieu (1818-1879) was the most famous forensic medical man of the mid-19th century. He was Dean of Medicine at the University of Paris. His book, *Etude Medico Legale*, reached its 6th edition in 1978. He is better known for his writings on battered child syndrome (Tardieu's syndrome).

¹⁹⁷⁷ Paul Camille Hippolyte Brouardel (1837-1906) was a French pathologist and professor of forensics at the University of Paris.

¹⁹⁷⁸ See Dubowitz and Bennett (2007) and Gilbert ea (2009a,b).

¹⁹⁷⁹ Posing for pornographic movies/photographs should be included.

effects on any aspect of the child's development.¹⁹⁸⁰ Incest is variously defined by statute as a specific sexual act¹⁹⁸¹ performed between persons who are prohibited to marry. It should not be forgotten that sexual abuse can occur at any age, including in old age, and childhood abuse of any variety may predispose to abuse as an adult.(Coid ea, 2001).

Under the *Punishment of Incest Act 1908* a male perpetrator of incest can receive a life sentence whereas a female perpetrator can only be gaoled for up to 7 years.

Under the Irish *Criminal Law (Sexual Offences) Act 2006* the age for consent for sex for males and females is set at 17 years. Anyone defiling a person under 15 years of age will receive a life sentence; those defiling someone aged 15-17 years will receive up to 5 years in prison, double that period if the perpetrator is a person in authority over the victim. Consent is not a defence where the victim is less than 15 years old, but an honest belief that the victim was over 17 years may be allowed as a defence in the case of older children.

Estimations of the incidence of CSA vary considerably (Johnson, 2004) with time, place, definition (e.g. emphasis on incest) and methodology.

England

Estimates from police records - incidence of 6.6/million population in late 1970s

Over 100,000 cases a year in US in early 1980s

USA

One-fifth of female and one-tenth of male college students reported having some type of sexual experience (incl. exhibitionism) with much older person during childhood

Two million children run away from home annually, perhaps up to half of them because of abuse, primarily sexual

Up to 70% of prostitutes report childhood incest and/or rape

Incidence of violence in general (incl. physical/sexual abuse of minors, assault, suicide and homicide) is said to be common among Native Americans (Indians) (Nelson ea, 1992)

Australia

History of CSA in 5.9% of women and 2.5% of men

Ireland

About 1.2/1000 Irish children/year are CSA victims

50% of reported cases are confirmed¹⁹⁸²

McGee ea (2002) identified 16% of men and 20% of women in Ireland as having been victims of CSA

New Zealand

In a study of 16-27-year-olds, child protection agency history for maltreatment (abuse and neglect) is significantly associated with a range of subsequent mood, anxiety, and substance use disorders (Scott ea, 2010)

Views vary on the frequency of inter-sibling incest vary between those who believe it to be the commonest form of incest to those holding that its frequency has been exaggerated. Clinical experience may be with the most damaging or damaged cases of incest. Father-daughter incest, the most frequently reported form, often starts when the girl begins to develop adult sexual characteristics. Mother-offspring incest and other forms of female-perpetrated CSA are not as rare as was once believed and the perpetrator is not necessarily psychotic; in fact, society may have conspired against accepting the existence of incestuous mothers.

¹⁹⁸⁰ Of infant homicides, 6 of 10 are killed by the mother. The *Medea complex* refers to killing of a baby to spite a partner/spouse. Killing of a baby within a day of birth may involve mothers from problematic homes who hide their pregnant state from others. Some mothers may abandon the baby. Abduction of a child may reflect custody disputes, sex slave traffic, kidnapping (e.g. for ransom), or so-called baby-stealing, the latter usually being a female crime and may involve a psychotic woman with delusions (perhaps messianic) about the infant, an intellectually disabled woman who seeks comfort from the baby, or someone who uses the baby to influence her partner (e.g. she may feel insecure after a miscarriage and tell her partner that the baby is theirs).

¹⁹⁸¹ Usually involving some form of intercourse.

¹⁹⁸² Garda Commissioner in 1920s reported that CSA of girls under age of 14 was reported in only 25% of cases, only 15% of cases being prosecuted.(Ferriter, 2004, p. 324)

Female abusers may represent in excess of 10% of perpetrators¹⁹⁸³. Homosexual incest (e.g. father-son) is usually seen in very disturbed families with violent, alcoholic or psychopathic fathers, a dependent mother, and disrupted of roles and identities; it is rarely reported - the daughters are often also abused by the father in such cases. Abused sons may become violent towards themselves and others. It has been reported that males comprise between one-sixth and one-half of the total numbers of adults reporting CSA and that male children are more likely to be abused outside the family and to come from neglectful homes and those that were mother-headed. Casey and Craven (1999) wondered if boys were really abused less often than girls, and pondered about the possibility that abused females might simply be more likely to disclose the abuse. According to one estimate, the relationship of the perpetrator to the child victim is father in half of cases, step-father in 17%, father and mother in 2%, mother's boyfriend in 7%, uncle in 7%, grandfather in 6%, and brother in 11%. The age distribution of CSA victims in a 1989 Irish study, wherein almost a quarter of perpetrators were under 16 years of age, was 32% of victims aged 1-5 years, 44% aged 10 years, 21% aged 11-15 years, and 3% aged 16 years. A broader view of CSA from abroad revealed that most perpetrators are men known to the child, are often in authority positions¹⁹⁸⁴, and 'contrary to popular opinion, relatively few come from the child's immediate family'.

Abuser characteristics: CSA occurs in all socioeconomic groups. Many if not most adult child abusers may start abusing children when they themselves are still adolescents. Alcoholism is reported very frequently among those convicted of incest. Mental illness is unusual, IQ is usually normal, but personality disorder is common. In one random community sample, a childhood history of a disrupted home, substance abuse, suicidal behaviour, inadequate parenting, and physical abuse were associated with women who had experienced CSA. The long-absent man returning to an unfamiliar and aging wife and a teenage daughter, the bereaved husband, the overcrowded home, the socially or geographically isolated family, the rejected spouse, and psychopathy, increase the chances of father-daughter incest. Incest families compared to non-incest families demonstrate a rigid internal belief system, a dysfunctional parental coalition, parental neglect and emotional unavailability, and an inability to nurture autonomy in its members. Brother-sister incest is often the result of poor adult supervision, although, in the authors' experience, the parent(s) may also be involved, as may, rarely, children living in the neighbourhood. It should be noted in passing that about 10% of paedophiliacs¹⁹⁸⁵ are bisexual in orientation. Most are heterosexual and many have a personal history of CSA.

The spouse may promote the relationship or deny its existence. She may report it after a row and then stand by her partner. In fact, she is rarely the reporting party. In the authors' experience, this fact has attracted varying judicial interpretations, varying from compassion to condemnation.

The act: Sexually abusive behaviours include genital exposure, fondling, masturbation, fellatio, and cunnilingus, digital penetration of the anus or vagina, or penile penetration of the vagina. The father may simply lie with her with no intention of incest at first. Later there is masturbation and inter-femoral intercourse. The average length of such a relationship in one Northern Ireland study was eight years. Psychoanalysts stress a potential need of the child to subconsciously view the abuser as good, allowing a turning to the perpetrator for relief of distress; also, the abuser may find it essential to be seen as good by the child victim rather than as a predatory seducer.

Diagnosis: CSA can present in a wide variety of ways. CSA usually presents in one or more of 5 ways: an account by the child; disturbed or altered behaviour; physical signs or symptoms; by association with other forms of maltreatment; and through allegations by parents, relatives or other adults.

Pointers to possible CSA

Over compliant or pseudomature behaviour

¹⁹⁸³ A study of US males (Holmes, 2007) aged 18-49 years in which two-thirds of the sample participated showed that men from one-parent families were more than twice as likely to report having been sexually abused as those from two-parent families. The former were more likely to be abused by a female and a non-relative (female baby-sitters were alleged perpetrators in several cases) whilst those from two-parent families were more likely to be abused by a male and a relative.

¹⁹⁸⁴ Teachers, activity leaders, family friends, etc. The UK *Kerr/Haslam Inquiry*, published in 2005, concerns sexual abuse of patients by two male psychiatrists in North Yorkshire. According to Kennedy, (2006) 3-6% of doctors internationally have engaged in intimate sexual contacts with patients (without assault) and psychiatrists, GPs and gynaecologists may be at relatively high risk.

¹⁹⁸⁵ A small number of children are abused by 'sex rings', i.e. groups of paedophiles.

Acting out, aggressive or regressive behaviour, running away
 Hints about sexual acting out
 Persistent and inappropriate sexual play with peers or toys, seductiveness
 Detailed and age-inappropriate understanding of sexual behaviour
 Lack of trust
 Poor or deteriorating school performance
 Excessive fear of males
 Sleep disturbances
 Depression and suicidal ideas¹⁹⁸⁶
 Pregnancy
 Discharge (vaginal, urethral)
 Bleeding (vaginal, rectal)
 Sexually transmitted disease
 Psychosomatic and behavioural problems (abdominal pain, drug overdose, anorexia, encopresis, and enuresis)

A complicated course of bipolar disorder (drug misuse, early onset, attempted suicide) may be linked to various forms of abuse in childhood.(Garno ea, 2005) Certainly, the combination of PTSD (with reports of physical or sexual assault) and bipolar spectrum disorder significantly interferes with social functioning.(Neria ea, 2008) Psychosis in adult females should prompt enquiry about abuse of any type in childhood.(Fisher ea, 2009)

About 70% of children who have been sexually abused have no abnormal physical signs. The report of the enquiry into CSA in Cleveland in 1987 stated that *abnormal physical signs are rarely unequivocally diagnostic, with the exception of the presence of semen or blood of a different group to that of the child.* Reflex anal dilatation¹⁹⁸⁷ occurs in 14% of children, in most of whom abuse is not suspected.

On interviewing the child, the same principles as in the general psychiatric examination of a child should be used, and the child's spontaneous account should be acquired; repeated probing sessions are unhelpful and potentially harmful. The child psychiatrist should approach the interview with an open mind and, if a family interview has been conducted, an interview with the child should be conducted on his/her own. The psychiatrist should steer a course between the extremes of overly leading questioning and, on the other hand, being insufficiently enabling for the reluctant child. Toys and other materials may assist recall. Use of anatomically correct dolls requires special training, and video tape recording reduces the need for repeated interviews, although some children may find the latter inhibiting. Written records should be kept and must be compiled at the time of the interview.

Sequelae and adjustment: Abused females are at increased risk in adulthood for personality disorders (and earlier conduct disorder), anxiety (including panic: Goodwin ea, 2005) and depression¹⁹⁸⁸ (Kendler ea, 2004), self-harm¹⁹⁸⁹, suicidal ideation, alcohol and/or substance abuse and dependence¹⁹⁹⁰,(Nelson ea, 2006) increased sensitivity to stressful life events,(Kendler ea, 2004) and frigidity or sexual aversion.

Women who have experienced CSA are at risk for posttraumatic stress disorder which may be associated with diminished anterior cingulate blood flow on positron emission tomography during traumatic script-driven imagery and whilst recalling memories of the abuse. Summit (1983) described a 'child sexual abuse accommodation syndrome' wherein the victim keeps the abuse secret for fear of terrible consequences that might follow its revelation; secrecy carries the risk of being helpless to avoid further abuse; maladaptive behaviour with negative effects on personality development; disclosure, when it eventually occurs, is

¹⁹⁸⁶ Suicide attempts, without apparent explanation, especially among teenage girls, should raise suspicion of CSA. The connection between later depression and CSA seems to a general and non-specific one and allowance must be made for the activity of other variables.(Maniglio, 2010)

¹⁹⁸⁷ With child in lateral position, dilatation of anus when buttocks are gently parted.

¹⁹⁸⁸ This depression may be associated with smaller hippocampal volumes (Vythilingam ea, 2002), although PTSD may account for a greater reduction in size than does the CSA.(Bremner ea, 2003) Gershon ea (2008) found that gender differences in the prevalence of such internalising disorders as depression did **not** seem to be attributable to differences in victimisation during childhood.

¹⁹⁸⁹ A history of sexual abuse, together with a dysfunctional family of origin and imprisonment of self or other, has been correlated with repeated self-harm.(Keeley ea, 2003) In a meta-analysis (Klonsky & Moyer, 2008) found no direct relationship between CSA and non-suicidal self-injurious behaviour; instead, there is a modest relationship due to correlation with the same psychiatric risk factors.

¹⁹⁹⁰ Including a positive family history of alcohol misuse.

delayed and therefore more difficult to believe; and the person may then retract the allegation to prevent breakup of the family unit.

Worldwide 21-country¹⁹⁹¹ study: childhood adversity and persistent suicidal behaviour (Bruffaerts ea, 2010)

Interviews to record childhood adversities predating age 18 years

Suicidal behaviour = thinking, plans and attempts

Increased risk of suicidal ideation and attempt associated with childhood adversities

Sexual and physical abuse were the strongest risk factors for onset and persistence of suicidal behaviour, especially during adolescence

There is evidence that female CSA victims may have a sensitised anterior pituitary and counter-relative adaptation of the adrenal cortex that is independent of major depression. On subsequent exposure to stress, these women hypersecrete CRF/CRH that in turn leads to down-regulation of adenohipophyseal CRH receptors and symptoms of depression and anxiety. The TAT haplotype¹⁹⁹² of the CRH receptor 1 (CRHR1) gene may offer protection against adult depression in females following maltreatment in childhood. (Polanczyk ea, 2009)

The incidence of unconsciously motivated ('conversion') non-epileptic seizures has been shown to correlate with CSA, and in particular with the degree of sexual penetration and closeness of relatedness to the perpetrator. Reported also was an excess of CSA in the personal histories of patients with generalised tonic-clonic episodes. A New Zealand study of women who had experienced CSA reported an excess of immature defence styles (displacement, passive-aggression, somatisation, and projection, but, interestingly, not dissociation), increasingly so with the severity of abuse.

One theory holds that women internalise their own abuse with resultant problems such as eating disorders, whereas men may externalise by abusing others. One study of referrals to an eating disorders clinic found that 30% had a history of CSA and 52% were rated as personality disordered, and CSA figured more prominently in women with disorders of personality than in those without such disorders. However, others find no support for CSA as a risk factor for bulimia nervosa. CSA may be a vulnerability factor for psychiatric dysfunction in general but not for eating disorder in particular. However, a history of CSA may worsen and complicate the course of eating disorders.

Cause-effect relationships between CSA and later psychiatric problems in victims are very difficult to establish with certainty.¹⁹⁹³ CSA may have a stronger affect on adult depressive symptoms in adults with certain alleles, i.e. Met allele of BDNF gene and S carriers of the 5-HTTLR polymorphism. (Aguilera ea, 2009)

In a study looking at two groups of adult women, a non-clinical sample and an outpatient sample, the possibility of a good adjustment appeared strongly associated with the nature of the abuse experience. Non-forceful, non-intrusive, and rare or infrequent sexual contact, were the least likely to cause lasting harm. With more severe forms of sexual abuse, however, few women were able to avoid persistent ill effects. Those who experienced forceful, repeated, or prolonged abuse or severe physical violation, and especially those abused by much older men, especially at the hands of fathers or stepfathers, were very likely to report persistent sexual problems in adult life. Depression may also be somewhat more likely in women, who experience CSA, especially if it involved attempted or actual penetration. CSA may be associated with long-term hyper-reactivity of the hypothalamic-pituitary-adrenal axis and autonomic nervous system, similar to that found in depressive states, especially in females; and stress in adulthood could then be more likely to provoke depression.

Spataro ea (2004) conducted a prospective study of boys and girls to determine the subsequent levels of treatment by public mental health services for mental disorder. Victims of both sexes had higher rates of treatment than did general population controls (12.4% v 3.6%) and rates were higher for childhood mental

¹⁹⁹¹ These did not include Ireland or the UK.

¹⁹⁹² TAT haplotype is formed by rs7209436, rs110402, and rs242924.

¹⁹⁹³ CSA is reported as being over-represented in a number of disorders, e.g. irritable bowel syndrome.

disorders, anxiety disorders and major affective disorders, but not for schizophrenia. Male victims received treatment more often than females (22.8% v 10.2%).¹⁹⁹⁴

Abuse by fathers or stepfathers may have a more negative impact than abuse by other perpetrators. Only a small percentage of women subjected to severe abuse reported that these experiences had no lasting effects. Actual genital contact, especially if prolonged and penetrative, and the use of force seem more traumatic for the victim. When the families do not support the victim or if the victims were taken out of the home, the outlook may in fact be worse. Adult women sexually abused as children show increased rates of depression, self-destructive behavior, anxiety, low self-esteem, feelings of loneliness, drug abuse, and a tendency to re-victimisation. In one study, women who had been abused as children, when compared with controls, were more depressed, anxious, and fearful; fear and distrust of men, and difficulty with sexual functioning were the most common reported long-term difficulties.

Children with disability are at increased risk of all types of abuse; language delay is common in child victims of CSA; and developmental delay may be a consequence of CSA.

According to American follow-up research on abused children, data on whether they are removed from or returned to their parental is not often recorded. They may spend years in 'temporary' accommodation awaiting a judicial decision, and if they are offered up for adoption there are few families willing to accept them.

A history of physical and sexual abuse in childhood is common in the histories of criminals. Similar findings have been reported for adults with conversion disorder.(Roelofs ea, 2002)

Transgenerational abuse (TA): The rule of one-thirds has been applied to whether child sexual abuse (CSA) victims grow up to abuse their children: one-third does, one-third doesn't, and one-third might do it if stressed. Salter ea (2003) followed up 224 former male victims of sexual abuse over 7-19 years and found that 26 (11.6%) became abusers themselves, typically abusing children from outside their own families. Childhood risk factors for later perpetrator status included material neglect, lack of supervision, sexual abuse by a female, witnessing serious violence at home, and cruelty to animals. Protective factors were not discernible, despite the fact that the majority did not become 'victim-abusers'. Such resilience probably stems from a combination of genes, environmental factors and willpower.(Bouvier, 2003)

Legal: Hefty prison sentences await the perpetrator, but only a minority of cases are detected and less reach conviction; and some cases may only be detected during the investigation of unrelated offences.

Children's and Young Persons Act, 1969

England and Wales

Social services must inform police of suspected CSA

Mistaken professionals, reporting in good faith and with due care, have been offered protection against legal redress for longer in Britain than in Ireland

Court of Appeal ruled (August 2003) that children can sue healthcare trusts and local authorities that wrongly conclude that they have been the victims of abuse (Dyer, 2003)

Protection for Persons Reporting Child Abuse Act, 1998

Ireland

Came into operation in January 1999

Persons (acting reasonably and in good faith) reporting to designated officers of health boards (medical staff, social workers, psychologists, substance abuse counsellors, physiotherapists, and radiographers) or Gardaí are protected from civil liability

Malicious reporting: fine of £15,000 and/or 3 years imprisonment

Employers cannot penalise the reporter

Various provisions for appeal by/against employers

¹⁹⁹⁴ Of course, some of the controls may have been abused and perhaps only the most seriously abused may have been brought to the attention of the authorities.

Irish Department of Health and Children may be preparing a White Paper aimed at enforcing mandatory reporting of child abuse

Professionals in Ireland should notify the local health authority (Community Care) and/or Gardaí of suspected physical or sexual abuse or wilful neglect of minors without waiting for confirmatory evidence. (Department of Health & Children, 1999)

Mandatory reporting (after Gilbert et al, 2009b)

For: improves awareness and better information on the problem can be accumulated; promotes early reporting; child protection agencies receive more reports; stresses official seriousness; furthers debate on ethical and legal issues

Against: swamping of services; inhibits reporting by parents in case they lose control of child's future; vulnerable people are over-reported; avoids development of community supports for children; greater emphasis on investigation than on intervention; professionals may pass on the problem rather than share it; subjectivity regarding threshold for reporting

Culturally sanctioned female genital mutilation, (Morris, 2006) widespread in Africa, is increasingly likely to be encountered in the West, and research is needed into its psychological effects and legal implications.

'False memory syndrome' (FMS)/ factitious CSA dilemma

No absolute test of trustfulness in a private crime, shrouded in secrecy

Untruthful allegations may be more likely with custody and visitation disputes and when constructing a legal defence

In terms of child abuse generally, untruthful allegations of child abuse occur in about 5% of evaluated cases

Can destroy professional careers

Complaints of CSA may be true, partly true or false (Dyer, 2005)

False accusations have been knowingly made by child's mother (Rand, 1996)

Professionals should keep an open mind

Confrontational methods of extracting 'memories' of CSA are fraught with pitfalls and can harm the innocent

Hypnosis aids recall of both true *and* confabulated memories

Factitious rape, stalking, and amorous attraction are not unknown

Management: This includes individual and family psychotherapy, anti-androgen compounds such as cyproterone in selected cases, the management of other problems such as alcoholism, and safeguarding of younger siblings. Psychotherapeutic strategies to help abusers include taking responsibility for the abusive behaviour, identifying patterns of ab, learning preventive measures, victim empathy training, and learning how personal abuse may be shaping abusive behaviour.

The abused child must be helped to relinquish previously necessary but now redundant emotional coping strategies such as dissociation and self-blame, including guilt over any sexual satisfaction derived from the abuse. Denial is facilitated by the secrecy surrounding abuse. Therapists must recognise and contain the victim's anger (or muteness), handle their own feelings, and be cognisant of the reflections of past relationships in the transference, including role reversal of abuser-abused relationships¹⁹⁹⁵. A process akin to grieving must be negotiated before the abused can begin to live with abusive memories in some sort of tolerable way.

¹⁹⁹⁵ Child subconsciously assumes role of perpetrator and assigns child's role to therapist.

Based on a review of twelve studies, Ramchandani and Jones (2003) concluded that the best evidence of efficacy for improving psychological symptoms in sexually abused children was for CBT¹⁹⁹⁶, especially for young children.

Group therapy of sexually abused adolescent children more benefit girls more than boys, the latter often being vulnerable, needy and sexually aggressive and perhaps in denial.

Caution must be taken against professional over-reaction where knee-jerk actions are taken to confirm suspicions and without considering options for the child. Also, be wary of under-reaction: not believing the child and taking no action to protect the child. The protection and best interests of the child must remain paramount. Case conferences are necessary, as liaison can be critical. To remove the child or perpetrator from the family home, how best to screen prospective employees in sensitive occupations and how to supervise carers are perennial questions and these must be answered in context. Electronic tagging of paedophiles is practiced in some countries: the police know if the paedophile strays beyond certain geographical limits. Extreme measures such as castration are practiced in some jurisdictions, e.g. California.

Some preventive issues: Children should know about appropriate and in-appropriate touching. The employment of the sexual attractiveness of minors, for example in fashion magazines, should be critically re-examined. Governmental support for families is important. There is evidence that male babysitters and stepfathers may be more abusive than female babysitters and biological fathers.

Comments: Early research concentrated on incest, only later enlarging its purview to include CSA outside the nuclear family. Abuse by teachers and religious and of those placed in care, the subject of intense media coverage, has hardly been researched at all in the scientific literature.

The childhood profile of those who eventually developed the strongest suicidal behaviour in a 21-year follow-up New Zealand study was characterised by the accumulation of many adverse social, family, personality, and mental health factors, only one of which was CSA. Those who were abused often denied it had happened. Childhood sexual and physical abuse is associated with later alcoholism, but such abuse is also associated with a family history of alcoholism, especially in the father. Suicidal ideation in a community sample of women with major depression was associated with a history of childhood physical abuse.(McHolm ea, 2003)

The great majority of fathers do not abuse children and the quality of parenting by **both parents** is a factor in determining risk of CSA by biologically unrelated perpetrators. Preliminary work with non-abusing parents of CSA victims is suggestive of a positive effect on psychopathology in both themselves and their children.(Forbes ea, 2003)

Elder abuse

Elder abuse/maltreatment or ‘granny battering’, abuse of an older person within a relationship normally based on trust, has only received attention since the mid-1970s and doctors¹⁹⁹⁷ are not as familiar with the concept as they are with, say, child abuse. A majority of cases are not reported. Definitions are unclear, there are no pathognomonic indicators, patients may conceal abuse, cases may not hold up in court when ‘beyond reasonable doubt’ is required of evidence, and professionals may accept or deny it. %. According to Hirsch & Vollhardt (2008, p. 734), depending on methodology¹⁹⁹⁸, the community prevalence of elder abuse has ranged from 1.2% to 10.8%. However, Cooper ea (2009) conducted a cross-sectional survey of English¹⁹⁹⁹ family carers of demented relatives living at home and found that 52% of carers reported some abusive behaviour and 34% reported more significant levels of abuse, whereas only 1.4% (3 carers) reported occasional physical abuse. The authors point out that those who practiced the most abusive behaviour may not have reported it.

¹⁹⁹⁶ Abused children with PTSD may benefit from a **trauma-focused CBT** comprising psychoeducation (teach child and caregiver ways of avoiding abuse), anxiety management (relaxation to reduce fear in response to abuse-related memories), exposure (talk, drawing, writing to gain mastery), and cognitive therapy (replace cognitive distortions and self-blame).(Cohen ea, 2000)

¹⁹⁹⁷ Medical students may misclassify non-abusive measures, such as exit camouflage to prevent egress, as abusive.(Thompson-McCormick ea, 2009)

¹⁹⁹⁸ *Action on Elder Abuse* (2007: www.elderabuse.org.uk) reported 62,000 cases of physical abuse, 86,500 cases of financial abuse, 105,000 cases of neglect, and 42,000 cases of sexual abuse in the UK. The *Mental Capacity Act 2005* in England makes it an offence to wilfully neglect or ill treat someone who lacks capacity.(Williams, 2008) The *Adult Support and Protection Act 2007* in Scotland more specifically protects vulnerable adults.

¹⁹⁹⁹ London and Essex.

Perpetrators include spouse, adult children and other persons/organisations who occupy caring roles. Perpetrators may suffer from alcoholism or psychiatric disorders. Care giving may lead to an excessive burden and depression in the carer. (Cooper ea, 2010) Carers, who may be financially dependent on a sick relative, often give up important parts of their lives in order to care and this may lead to emotional difficulties, social isolation, and physical exhaustion. An early abusive relationship between carer and patient may antedate current mutual abuse. Abuse may be triggered by, e.g. stress in the carer or incontinence or dysphasia in the victim. Multiple forms of maltreatment constitute the commonest scenario and a sense of helplessness compounded by passivity on everyone's part often complicates matters. Victims are often unable to defend themselves. They may have a physical or psychiatric disorder, including cognitive disorders. The abused elder may become disturbed which may lead to further abuse. Abuse may arise from acts of commission (physical, psychological/emotional, financial) or of omission (neglect and abandonment).

Institutional abuse, as in hospitals and nursing homes, takes many forms and includes loss of personal power in an excessively authoritarian environment, poor staff levels and wages, burnout, underappreciated work, poor training and supervision, over-large facilities, and stresses in the personal lives of care workers. Aggressive behaviour in the patient may predate retaliation by staff. Abuse may be inherent in cultural values, as when it is assumed that being old is synonymous with lack of competency (infantilization) and a drain on societal resources.

Some pointers to elder abuse

General – repeated admissions, restricting visitors, forcing elder to live where he/she does not want to live, e.g. a care home

Physical – bruising in strange places like wrists or soles, cuts, injuries of various age, bilateral injuries, restraint injuries, occult fractures, over-medication, broken spectacles or hearing aid, etc

Psychological – inconsistent history, unusual behaviour/mood

Sexual (O'Brien & Smock, 2003; Kennelly ea, 2007) – injury to breasts/genitalia, rectal/vaginal bleeding/bruising, STD, etc

Financial – stealing, bank account violations, not filling prescriptions or other poor care despite having money to meet such needs, etc

Neglect – delayed help-seeking, infantilization, irregular/excess/inadequate medication, decubiti, malnutrition, severe weight loss, dehydration, poor hygiene, dirty home, unsafe stairs, etc

Iatrogenic – ageism, not paying heed to dignity issues, etc

The Irish Health Services Executive (HSE) elder abuse service²⁰⁰⁰ originally received about 1,500 referrals²⁰⁰¹ over 12 months, 10% of which were notified to the police²⁰⁰². 83% of referred people lived at home and the vast majority (965) of cases involved intrafamilial abuse. Further details are given in the box.

Health Service Executive (HSE) elder abuse service 12-month referrals (Mulholland, 2008)

Type of abuse – 29% psychological; 21% neglect; 20% financial; 17% physical

Referrers – 34% community healthcare staff; 23% other HSE staff; 11% family

HSE elder abuse service 12-month referrals for 2009 (Mulholland, 2010)

1,870 referrals of which 435 were for self-neglect only – of remaining 1,435: 34% psychological; 22% financial; 20% neglect; 14% physical

Alleged perpetrators: 46% son/daughter; 20% other relative; 18% partner/husband/spouse

Elder abuse (including excessive coercion and sedation in institutions), which is more often chronic than once-off, should not be tolerated and society must canvass for protection of its elderly. Blame is not constructive and is best avoided, unless referral to the legal authorities is considered necessary. The media should highlight the problem in a constructive way. Victims should receive treatment for any psychological or physical damage incurred and protection at a level commensurate with past abuse and the likelihood of

²⁰⁰⁰ The HSE launched a campaign called 'Open Your Eyes' in 2008 order to raise awareness of elder abuse.

²⁰⁰¹ Acknowledged as not reflecting elder abuse in total.

²⁰⁰² Referral to Gardaí (Irish police) depends of elder's wishes and type of alleged abuse.

its persistence. Photographs of injuries should of forensic standard. Multidisciplinary team involvement is necessary to ensure that all needs are recognised and, as far as possible, met. Everyone involved should be interviewed alone and collectively. Communication, problem-solving, and conflict resolution skills should be thought. Acknowledging the difficulties inherent in caring may lead to open admission of shortcomings. Day care, respite admission, nurse visitation, and home help are among the interventions to be considered. The GP must be informed of the findings of any assessment. Good documentation of decision-making pathways is important if the clinician is wrong about abuse having occurred.(Williams, 2008)

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17

Psychosexual medicine²⁰⁰³

Brian O'Shea

'Sexuality is a social construction, and medicalisation is the new social construction'. (Tiefer, 2002)

Unfortunately, training in psychosexual medicine amongst psychiatrists is often poor and few of them feel comfortable the psychosexual aspects of clinical work. (Rele & Wylie, 2008) DSM-IV and ICD-10 artificially divide up sexual disorders in a way that does not reflect clinical practice. For example, it is not uncommon to see a male patient who has both premature ejaculation and erectile dysfunction or a woman with combined hypoactive sexual desire (low sex drive) and vaginismus. Concerns have been rightly raised that we may pathologize sexual problems. Low or absent desire may reflect problems in a relationship and some difficulties may be relatively mild and transient.

Gonadal and secondary sexual differentiation

Genetic sex is determined at conception. During the first weeks of pregnancy the gonads are undifferentiated. A Y chromosome causes testicular development through the agency of H-Y antigen. Absence of Y chromosome or H-Y antigen leads to ovarian development. The presence or absence of foetal androgen (from any source) determines genital development. Foetal androgen in a genetic female, such as occurs in adrenal hyperplasia, leads to male genitalia, even if ovaries are present: the baby has male or ambiguous genitalia. Even in a foetus with Y chromosome and testes, absence of foetal androgen, as occurs when an enzyme is deficient, or the presence of abnormal androgen receptors, such as happens in testicular feminisation, lead to female genitalia.

Congenital adrenal hyperplasia: *In this inherited condition²⁰⁰⁴, a girl (genetically females with ovaries, etc) produces excess androgens whilst still in utero and is born with masculinised external genitalia. If the latter are surgically corrected in infancy the girl will have a female gender identity and role; if not corrected, she will view herself as being male and act as such. This condition flies in the face of theories that androgenisation in utero influences the formation of gender identity. Psychological adaptation studies variously report no excess (Morgan ea, 2005) or an excess (Slijper ea, 1998) of psychiatric morbidity. In real life, most probably cope well, others finding life difficult. Barriers to help-seeking need to be overcome.* (Cull, 2005)

Imperato-McGinley syndrome: *This condition was described in 1979. Testosterone is converted to dihydrotestosterone by testosterone 5- α -reductase. Testosterone is thought to masculinise the brain and internal genitalia, and dihydrotestosterone to masculinise the external genitalia. The chief source of androgens in females is the adrenal. When there is a deficiency of testosterone 5- α -reductase the production of dihydrotestosterone does not happen, with a resultant female appearance to the external genitalia at birth. Virilisation occurs at puberty. These people have a heterosexual male gender identity and psychosexual orientation.*

Normal range of sexual responses

The normal sexual response of the mature male consists of a baseline followed by excitation to a plateau phase that culminates in orgasm²⁰⁰⁵. Orgasm is succeeded by a refractory (to further sexual excitation) period during which there is sexual quiescence. The female response is similar with the exception of the absence of a refractory period. The longer resolution phase in the female may occasionally cause problems if the partner simply goes to sleep after sex. It should be noted that the normal outer one-third of the vagina narrows and the inner two-thirds dilate when the woman becomes sexually excited.

Ejaculation is mediated via the sympathetic nervous system and the thoracolumbar spinal cord²⁰⁰⁶. Orgasm in both sexes involve involuntary contractions in both internal and external sphincters with, in addition, 4-5 contractions of prostate, seminal vesicles, vas

²⁰⁰³ Paraphiliacs usually have more than one deviation. The history is usually lengthy, presentation being for the one for which the person was arrested. The relapse rate is very high. Claims of being 'cured' may arise for legal purposes. Sexual crimes accounted for 1% of indictable offences in the Republic of Ireland in 1998.

²⁰⁰⁴ **Pseudogenes** are mutated gene duplications incapable of translation into functional proteins. They may misalign with a neighbouring normal gene during meiosis and a crossover may mutate the normal gene. An example is the mutation of the gene for 21-hydroxylase, leading to congenital adrenal hyperplasia.

²⁰⁰⁵ Orgasm may occur in some females with complex partial seizures whereas their male counterparts may only experience discomfort in the penis!

²⁰⁰⁶ Truitt and Coolen (2002) found a possible ejaculation generator in rat lumbar spine.

deferens, and urethra in males, and, in females, 3-15 contractions in lower vagina as well as sustained uterine contraction starting in fundus and spreading to cervix.

Orgasmic intensity may decline with age for various reasons, e.g. reduced strength of muscle contraction.

Sexual orgasm has been reported in humans of either sex when the septal area of the brain is stimulated directly. Stimulation of the posterior portion of the postcentral gyrus can give rise to genital sensations. Epileptic foci arising from the paracentral lobule can give rise to genital sensations as part of the aura. (Ike & Seagraves 2003, p. 339) Most patients with spinal cord injury fail to ejaculate, or if they do, it is either without orgasmic sensation or only with an awareness of some altered feeling. The majority of male paraplegics with spinal cord injury put resumption of sexual function first in their list of priorities. (Anderson, 2004) Patients with spinal cord injury often say that they develop an area of arousal lying superior to the level of the lesion leading to sexual satisfaction ('phantom orgasm') from tactile experiences such as a caress.

When a man is sexually stimulated the penile tissues produce nitric oxide²⁰⁰⁷ that then stimulates the release of guanylate cyclase, the latter triggering the conversion of guanosine triphosphate to cAMP; cAMP relaxes smooth muscle²⁰⁰⁸ leading to vasocongestion and penile erection. Phosphodiesterase 5 deactivates cAMP. Since the clitoris has no tunica albuginea the clitoris becomes swollen but not rigid.

Visual stimulation leading to an erection is accompanied by activation of claustrum, paralimbic regions, hypothalamus and striatum, whereas direct penile stimulation is associated with activation of the insula. (Georgiadis & Holstege, 2005)

Testosterone does improve sexual interest in hypogonadal men but it does nothing for sexual desire in males who already have enough testosterone. Very low testosterone levels in females (adrenalectomy, oophorectomy, menopause) may impair sexual desire and the administration of testosterone may improve matters, but most women with low sexual desire do not have excessively low testosterone levels and giving them testosterone may make matters worse (facial hair, acne, etc). (contrast Bhasin et al, 2007 with Heiman, 2008) A female testosterone patch (Intrinsa) is available for women with low sexual desire associated with distress who have had an early menopause due to hysterectomy and bilateral oophorectomy and are receiving concomitant oestrogen therapy. Oestrogen does not significantly affect a woman's sexual drive (Moynihan, 2005) and the evidence for progesterone is mixed. (Meston & Frohlich, 2002) Dopaminergic drugs like levodopa tend to increase sexual desire in males, and there is limited evidence for such an effect in females. Longterm use of opioids reduces libido in both sexes, possibly by decreasing testosterone and luteinising hormone (LH) levels. Sexual arousal in females is facilitated by the sympathetic nervous system. Sexually functional women and those females with low sexual desire show increased physiological sexual arousal after exercising (or if given ephedrine) if they were then shown an erotic film, exercise alone not being enough. Conversely, drugs such as clonidine (sympatholytic) impair sexual arousal. (Meston & Frohlich, 2002)

The mean reported onset of menstruation in a sample of Irish schoolgirls in 1990 was 12.5 years. (Fitzgerald et al, 1990) The mean reported onset of menstruation in Irish girls was 13.52 and 12.53 in 1986 and 2006 respectively. (O'Connell et al, 2009)

Women can remain clitorically responsive throughout life and can be multi-orgasmic at an advanced age and, unlike males, they have little change in the post-orgasmic refractory period, but they may face a scarcity of sexual partners, have vaginal dryness, etc. Sex is not confined to the young. (Kleinplatz et al, 2009)²⁰⁰⁹

There is little evidence for an andropause (the equivalent of the female climacteric in males). Gould et al (2000) suggested that androgen sensitivity develops in older men and might benefit from testosterone.

Masturbation is an almost universal practice that may be excessive under conditions of anxiety. Guilt over this practice is either cultural or depressive. Mutual masturbation, cunnilingus (blowing air into the pregnant vagina is a rare cause of death – embolic?), and fellatio are not abnormal *per se* and may form part of normal foreplay. Masturbation fantasies may play an important part in perpetuating deviant sexual behaviour. In such cases it is necessary to advise either neutral thoughts or ordinary heterosexual intercourse fantasies during the act.

Preventable causes of death in the US in 1990 included 1% of total deaths from high-risk sexual behaviour. One should not prematurely conclude that all sexual inadequacy in chronic mentally ill people is due to prescribed drugs. Such illnesses have a profound effect on psychosexual development and function, as have institutional life, intellectual disability, illegal drugs, lack of opportunity, and so on. Most effeminate boys grow up to be heterosexual, some will be homosexual, and transsexualism is the least likely outcome. Tomboyish behaviour in girls is less likely to cause parental concern than effeminacy in their sons.

We are living in a rapidly changing world. Cybersex (teledildonics) involves computer programmes of increasing sophistication designed to deliver 'virtual' sex to the user! The net is crowded with advice on how to improve one's sex life. One such promise is to deliver a larger penis! In fact, there are two procedures for doing so: division of the suspensory ligament that holds the penis to the pubic arch and injected fat removed from elsewhere. The first procedure leads to a slightly longer penis that falls forward and with hair on the shaft (pubic skin pulled forward), and the second gives an uneven, lumpy penis! (Bolton, 2005)

Sexual disorders in psychiatric practice are classically divided into the deviations and the dysfunctions. Before proceeding to deal with these conditions we will deal with the premenstrual syndrome (PMS).

²⁰⁰⁷ Nitric oxide (NO) seems to control tone in the vaginal smooth muscle and high NO levels are associated with better vaginal lubrication.

²⁰⁰⁸ Anoxia is thought to stimulate conversion of corporal smooth muscle cells into fibrocytes.

²⁰⁰⁹ **Sex in the elderly:** Doctors should enquire about the sexual lives of older people and older people generally want to be asked. Such enquiries normalise and affirm what has for too long been taboo. (Kleinplatz, 2008) Whilst older men think about sex, older women are more likely to be satisfied with intimacy. (Basson, 2000) Even if older people do not have sex it does not mean that they do not view it as important. (Gott, 2005) Lindau et al (2007) found that older US adults are often sexually active (M>F), they were less sexually active if they believed they had poor health, and those (common) with sexual dysfunction (M: erectile problems; F: low desire, dry vagina, inability to climax) infrequently spoke to a doctor about it. Relationship factors and mental health may be better predictors of sexual activity than physiology in older women compared to their male counterparts. (Bancroft, 2007) A Swedish study of 70 year olds found that the amount and quality of sexual experience has improved over a 30 year period. (Beckman et al, 2008)

The premenstrual syndrome (PMS)

The reason women complain about physical, psychological and behavioural changes during the week before menstruation are complex and aetiology is most likely multifactorial. Some symptoms do not cease with menstruation (hence the term 'paramenstrual') and some women experience mild symptoms during the follicular phase. In a study of over 40 women in Oxford during the 1980s, the symptoms of PMS disappeared in two-thirds of patients after hysterectomy (? primary psychological cause) and persisted, albeit less intensely, in the others (? primary physical cause). (After hysterectomy, certain core complaints, such as irritability and breast tenderness, may persist in cycles, suggesting a possible role for the hypothalamus or ovaries.) In an earlier study, two-fifths of PMS developed for the first time following pregnancy. A later twin study found evidence in favour of a genetic factor in the aetiology. However, a still later twin study could not distinguish between environment and genes; neither could it determine what was inherited, e.g. PMS itself or neuroticism. Other possible causes include dysregulation of the serotonin system²⁰¹⁰, hormones (low progesterone, high oestrogens, and raised prolactin), MAO, BDNF Met, a deficiency of pyridoxine²⁰¹¹, cyclical transient hyperparathyroidism²⁰¹², and activation of the renin-angiotensin - aldosterone system.

Epperson ea (2002) conducted an MRS study on PMS and healthy females. They found a relative reduction in cortical GABA levels during the follicular phase in the PMS group. Cortical GABA levels declined across the menstrual cycle in healthy women, whereas women with PMS experienced an increase in cortical GABA levels from the follicular phase to the mid- and late-luteal phases. Whilst some women are found to have thyroid dysfunction the consensus is that PMS/PDD is 'not a masked form of hypothyroidism'. (Steiner & Yonkers, 1998, p. 3)

Many physical (migraine, allergy, asthma, seizures, herpes genitalis) and psychiatric (depression, mania, psychosis, anxiety/panic, bulimia, drug abuse) disorders are exacerbated premenstrually. These conditions should not be confused with PMS. Ekebert ea (1986) found no relation of statistical significance between the day of self-poisoning and the menstrual cycle phase in a study of women with regular menstruation admitted for self-poisoning. However, the idea that women kill themselves or commit illegal acts²⁰¹³ more commonly in the premenstruum persists.

The term '*premenstrual dysphoric disorder*' (PDD – DSM-IV) may cover a much less common group than PMS does: 3-8% v up to 75% of women according to Steiner and Yonkers (1998) and as low as 1.3 according to Gehlert ea. (2009) However, Yonkers ea (2008) suggested that most cases of PMS meet PDD criteria. Gehlert ea (2010) state that while PDD shares somatic symptoms with PMS, its psychiatric symptoms preponderate and they suggest that PMDD might be seen as a psychiatric condition. PDD cases are very depressed, anxious, with labile affect, and have reduced interest in activities. Strictly defined, PDD occurs during the week before a period but never after one. However, at least 75% of women report minor or isolated premenstrual changes. (Van Leusden, 1995) There may be a deficiency of GABA.

Three to five percent of women (figures vary) report that at least one physical or psychological symptom reaches severe or temporarily disabling proportions during the week before a period. Some women's symptoms peak after the start of menstruation.

Clinical features of PMS

Physical - painful or tender breasts, feeling of being swollen, pain in head/ back, stomach cramps, rashes

Psychological - tension, depression, irritability, fatigue, insomnia, labile emotions, forgetfulness, feeling lonely

Behavioural - inefficiency, dropping things, accident-proneness, avoidance of social gatherings

DSM-IV premenstrual dysphoric disorder

²⁰¹⁰ E.g. tryptophan (5-HT precursor) depletion or use of methergoline (5-HT receptor antagonist) may exacerbate the symptoms. (e.g. Roca ea, 2002)

²⁰¹¹ Acts as a co-enzyme, pyridoxal phosphate, in DA and 5-HT synthesis.

²⁰¹² Reduced peri-ovulatory calcium levels and increased levels of parathormone levels (due to increased oestrogen before ovulation?) in PMS and premenstrual dysphoric disorder patients reported by Thys-Jacobs ea. (1995) Supplemental calcium (600 mg b.i.d.) might normalise fluctuations in calcium/parathormone, thereby regulating effects of calcium on neurotransmitters.

²⁰¹³ Malmquist (2006, p. 77) is not impressed by the level of evidence.

In the majority of menstrual cycles during the last 12 months: at least 5 of the 11 symptoms shown below are present for most of the last week of the luteal phase and they remit within a few days of onset of menstruation and are not present in the 7 days after the period (at least 1 symptom must be from 1-4)

1. Low mood/dysphoria
2. Anxiety/tension
3. Labile mood
4. Irritability
5. Reduced interest in usual activities
6. Poor concentration
7. Lack of energy
8. Significant changes in appetite, including craving food/overeating
9. Too much or too little sleep
10. Overwhelmed by everything
11. Other physical complaints, e.g. bloating or tender breasts

Symptoms must severely disrupt coping/relationships, not be an exacerbation of another condition, and diagnosis is prospectively confirmed by rating symptoms every day for at least 2 consecutive cycles

Management: A diary should be kept for a few months before and during treatment. Psychological problems should be sought and addressed.

Some proposed treatments for PMS

Placebo²⁰¹⁴

Supportive psychotherapy, marital counselling, other forms of psychotherapy

Treatment of any thyroid anomaly

Regular small meals to prevent hypoglycaemic tension

Multivitamins or vitamin B6²⁰¹⁵

Polyunsaturated fatty acids as in evening primrose oil²⁰¹⁶

Calcium carbonate

Exercise and relaxation

Pure progesterone

Combined oral 'pill'²⁰¹⁷

Oestradiol implants with combined cyclical progestagen²⁰¹⁸, oestradiol patches

Bromocriptine²⁰¹⁹

Danazol

Diuretics without potassium supplements

NSAIDs

Gonadotrophin releasing hormone analogues

Naltrexone

Light therapy may reduce depressive ratings. SSRIs, e.g. fluoxetine 20 mgs/day (continuously or from day 15 of cycle to several days after start of each period), are often effective for PMS.(Dimmock ea, 2000) Sertraline gives better results with longer treatment although relapse rates are still high and especially so if baseline symptoms are severe.(Freeman ea, 2009) It should be noted that after a decision by the European drug regulator that premenstrual dysphoric disorder was not 'a well-established disease entity', this indication was dropped from Prozac's (fluoxetine) data sheet in early 2004.(Moynihan, 2004) PDD may be a sounder argument for drug therapy than PMS. CBT may produce an effect that is slower in onset but lasts

²⁰¹⁴ Some say 50% response, range 20-80%., others putting it at 40-90%.

²⁰¹⁵ B6 may cause neuropathy with ataxia, numb hands and perioral numbness, if used in high dosage: > 2 G/day, or > 200 mgs/day in the long run – this may persist.(Tomkins, 1994)

²⁰¹⁶ Gamma-linolenic acid – used because some PMS cases have reduced blood levels of essential fatty acids; randomised controlled trials have not produced evidence of efficacy.(Steiners & Yonkers, 1998, p. 15)

²⁰¹⁷ This has made some cases worse and evidence for efficacy is lacking.

²⁰¹⁸ E.g. dydrogesterone.

²⁰¹⁹ Take at night because of side effects.

longer than SSRIs. (Hunter *et al.*, 2002) Alprazolam given in the late luteal phase²⁰²⁰ may help some cases. 'A simple approach', according to Massil and O'Brien (1986), would be to use an oral contraceptive for younger women who do not want to become pregnant, and a progestagen (e.g. dydrogesterone) for women unsuitable for the 'pill'. Both regimens may be combined with vitamin B6. Dydrogesterone (Duphaston) 10 mgs, b.i.d., from day 12 - day 26 of the menstrual cycle may be of benefit for those patients with multiple symptoms. Exercise helps. Alcohol and caffeine are best avoided before a period.

Rape trauma syndrome

This has two phases. (Burgess & Holmstrom, 1974) The short term (hours to days) is characterised by emotional shock, disbelief, despair at a life-threatening experience, and somatic symptoms, eating and sleeping problems, and emotional reactions such as mood swings, anxiety and depression. During the long term (months to years) the victim tries to reconstruct her life and relationships.

*Lesbian and gay people (homosexuality)*²⁰²¹

'The concept of unconscious homosexuality has been so exaggerated...that...there would be...only two types of men, those who are homosexual and those who think they are not'. (Jean Delay, quoted by Moussaoui, 2002, p. 99)

In the recent past, when homosexuality²⁰²² (HS; O'Shea, 2001; Kaplan, 2004) was considered a 'disease', various forms of 'therapy' were employed, including electrical aversion therapy (high voltage, low amperage), lysergic acid, chemical castration (with hormones), narcoanalysis, gender reassignment surgery (in South African military hospitals), and psychotherapy. Homosexuality may be less common than bisexuality.

Data from the USA in 1993 based on a national survey of men showed that only 2% of sexually active men had sex with other men during the preceding ten years, and only 1% were exclusively HS, figures significantly lower than in the classic, unrepresentative, and probably inflated, Kinsey²⁰²³ (Kinsey *et al.*, 1948, 1953) reports. Later Western studies of homosexual practices (Johnson *et al.*, 2001; Jorm *et al.*, 2002) found prevalence rates for males and females of 1-2.8% and 1.4-2.6% of males and females respectively. Too many studies have been confounded by recruitment in gay bars, and such results are unlikely to be typical of the wider population. Definitions of homosexuality vary between studies. In 1979 in the US 10% of adolescents were said to have experience of HS, whereas in 1994 in the UK 6% of 16 to 24 year olds had such an experience. HS activity is often transient in adolescence.

The nerve supply to the anal margin is the same as for the genitalia. Males who are raped by anal intercourse may be particularly upset if they experience erection and even ejaculation, not realising that this is a physiological response to pressure on the prostate. (Osterman *et al.*, 2003) One-third of HS males do not practice anal sex; one-third of British couples practice it occasionally and about 10% have it as the preferred or regular method; therefore more British heterosexuals practice anal sex than do gay men! Also, one in ten heterosexual couples in the US practice anal sex at least occasionally.

Since 1973, the APA has dropped HS as a disorder. Female transvestism is apparently very rare, and unlike male cases, these women are almost always HS.²⁰²⁴ The primary transsexual (always believed he is

²⁰²⁰ **Premenstrual dysphoric disorder (PDD):** DSM-IV-TR excludes mere exacerbation of symptoms of other disorders, e.g. depression or panic disorder, or indeed of personality style/disorder magnification. However, a woman may have the latter plus PDD. In women having menstrual periods, the *late luteal phase* occurs between ovulation and menstruation onset. The *follicular phase* starts with menstruation. In women without periods (including those who had the uterus removed) the timing of phases may need measurement of reproductive hormones.

²⁰²¹ Gay Doctors Ireland: gaydoctorsireland.ie

²⁰²² The term lesbian (syn. sapphism) comes from the island of Lesbos on which the poetess Sappho once resided. Another name for homosexuality in Krafft-Ebing's day was 'congenital inversion'!

²⁰²³ Alfred Kinsey (1894-1954), American biologist.

²⁰²⁴ **Homosexuality (HS) as a disorder:** Karl Heinrich Ulrichs (1825-1895) argued against German sodomy laws in a treatise of 1864 and suggested that HS represented a third sex. Ulrichs was fired as a legal adviser to a Hanoverian district court when it became known that he was homosexual. Karl-Maria Kertbeny (1824 [Vienna] -1895 [Budapest]), a journalist and another advocate of the dissolution of sodomy laws, coined the term 'homosexual' during the 1860s. Richard von Krafft-Ebing (1840 [Mannheim] – 1902) adopted Kertbeny's terminology but believed that HS was a degenerative disorder of the nervous system. In 1914 the German homosexual psychiatrist, Magnus Hirschfeld (1868-1935) added his voice to the third sex idea. The Nazis burned books taken from his *Institut für Sexualwissenschaft* in 1933. Sigmund Freud (1856-1939) saw HS as a normal phase in development but that its adult persistence was due to arrested development, i.e. fixation at an earlier psychosexual stage. Later, Sandor Rado (1890-1972), a Hungarian, viewed HS as a phobic avoidance of heterosexuality caused by problems with early parenting. Largely as a result of gay protests and studies such as those of Kinsey, the APA removed HS as a disorder from the seventh printing of DSM-II in 1973 but

female), unlike his secondary counterpart (later onset of belief in opposite sex status, e.g. during adolescence) does not have HS fantasies. The combination of HS and personality disorder makes for difficulties in interpersonal relationships, just as it does in the case of heterosexuality. Homosexual erotomania, the delusional belief that someone (who may even not know one) loves one, has been described in a patient with AIDS.

HS occurs from time to time in animals but exclusive HS is confined to humans. Most children who develop an HS orientation²⁰²⁵ have heterosexual parents. A small minority of HS only become aware of their orientation late in life, sometimes in the setting of a failing marriage or the responsibilities of parenthood, but most people know their orientation very early on. The determinants of sexual orientation and the timing of its development are poorly understood, and they are not necessarily the same in each sex. Most effeminate boys grow up to be heterosexual in orientation, and tomboyish behaviour in girls is less likely to cause parental concern. Psychoanalytic explanations for lesbianism have included a rejecting, emotionally distant mother and a powerful, frightening father. A minority of psychotherapists may still occasionally view homosexuality in a client as a pathology requiring treatment. (Bartlett *et al.*, 2001; King *et al.*, 2004) Some HS or bisexual people experience negative reactions to the discovery of their sexual orientation because of attitudes acquired from others, so-called 'internalised homophobia'. Awareness of homosexuality can surface at widely different ages for different people. A large controlled community study of retrospective accounts by HSs of their parenting found no major differences from those of heterosexuals. The finding that the adoptive brothers of HS twins were more prone to HS than their biological siblings favours an environmental role. Cultures accepting of HS may allow expression of HS and heterosexuality in the same individual. Cultures discriminating against gays and bisexuals may account, at least in part, for reports of high levels of mental disorder (especially in males: Fergusson *et al.*, 2005) in these people. (Warner *et al.*, 2004) Many women, and to a lesser degree men, seem able to change or modify their sexual preferences at different times during their lives.

In a study of identical and non-identical twins and the adoptive sisters of HS probands recruited through advertising in American lesbian-oriented publications, and after complicated corrections and assumptions were made, Bailey *et al.* (1993) concluded that the heritability of their sample was significant at over 25%. Hamer *et al.* (1993) linked male HS to the X-chromosome, but there are several methodological problems associated with this research. Baron (1993) stated that if HS was genetically determined it 'would have become extinct long ago because of reduced reproduction'. There are interpretative problems with twin research, and adoption studies are rare.

Two small groups of neurones in the human hypothalamus show sexual dimorphism (inter-sex differences), being nearly twice as large in men as in women. There is some evidence that these nuclei may also be smaller in male HS, which has been explained on the basis of circulating perinatal androgens. However, explanations which favour hormones as the chief source of gender identity²⁰²⁶ (person's concept of him/herself as male or female, as distinct from sexual orientation) must contend with the proven effects of rearing in people with difficult-to-assign sex²⁰²⁷ at birth. There is in fact no demonstrable hormonal difference unique to HS. Also, any reported difference in structure or function has to account for the feedback effect of HS itself! Similar problems bedevil research into anorexia nervosa.

HS is no longer illegal in Ireland. In England, the age of consent for heterosexuals is 16 years. It is also 16 years (reduced from 21 years in 1994 and 18 years in 1998) for male HS, despite House of Lords opposition²⁰²⁸. Custody and visiting rights are more likely to be granted to HS women than men. However, few cases come to court or are reported. There is a need for follow-up studies on children reared by HS couples. Children are just as likely to be sexually assaulted by a heterosexual parent as by a HS one. (King & Pattison, 1991) The British Parliament voted to allow unmarried couples, whatever their sexual orientation, to adopt children jointly. (Golombok, 2002) A number of jurisdictions now permit same-sex

replaced it with 'sexual orientation disturbance', i.e. ego-dystonic HS. The latter was replaced by 'ego-dystonic HS' in 1980 in DSM-III but was omitted from DSM-III-R in 1987. DSM-IV-TR contains 'sexual disorder not otherwise specified' (including persistent and marked distress concerning sexual orientation), 'identity problem' (can include uncertainty about sexual orientation/behaviour), and 'phase of life problem' (problems associated with phase of development or life circumstances not explicable by mental disorder).

²⁰²⁵ Sexual orientation is probably best viewed dimensionally, from exclusive homosexuality to exclusive heterosexuality. Most adolescents who engage in homosexual behaviour will become heterosexual adults.

²⁰²⁶ Gender identity develops early and is usually established by 3 years of age.

²⁰²⁷ E.g. women with congenital virilising adrenal hyperplasia.

²⁰²⁸ No special age for females!

marriages (and attempts to curb them – 1996 US *Defence of Marriage Act* defines marriage as a heterosexual matter: 26 US States ban same-sex marriages and a number of other US States offer civil unions) and some others offer marriage in everything but name²⁰²⁹.

Jurisdictions allowing same-sex marriage (SSM; gay marriage)

2001 – Netherland first country to allow SSM

2005 – Spain²⁰³⁰ (and Canary Islands) recognises equality between SSM and opposite-sex marriage

Belgium, Canada, Norway and South Africa

USA – Massachusetts and California

Most paedophiles are heterosexual: according to Meston & Frohlich (2003) 2% of the general population are homosexual as against 40% of paedophiles. Those who are stalked by people of the same sex as themselves get less consideration from law enforcement agencies that victims of opposite gender stalking. HS males have an increased risk for perianal carcinoma. Oral sex is relatively safe from the HIV point of view²⁰³¹, but carries the risk of contracting gonorrhoea and non-specific urethritis. Lesbians are at relatively low risk for HIV. Faeco-oral spread may involve Giardia and hepatitis A. Increased risk for hepatitis B indicates multiple partners rather than individual sexual practices.

King ea (2003) conducted a cross-sectional survey in England and Wales and found that gays of both sexes demonstrate an excess of psychological distress, saw a mental health professional more often, deliberately harmed themselves more frequently, and were more likely to use recreational drugs than were heterosexuals; lesbians were more likely to have experienced verbal and physical intimidation and to consume more alcohol than heterosexual women. Smith ea (2004) point out that, despite decriminalisation of HS in Britain in 1967, attempts to treat it continued, leaving many in distress.

If the problem is one of adapting to HS (or bisexuality) the therapist helps in clarifying thoughts, options and consequences. If the orientation is bisexual or mainly heterosexual and the client wants to 'be' heterosexual, the avoidance of HS cues (incl. thinking about it while masturbating), the seeking of closer liaison with the opposite gender (e.g. clubs), and thought distraction techniques could be advised. Lesbians may enquire about relationship problems such as jealousy, insecurity, or sexual dysfunction with other women, or indeed with a man in their lives. Despite Freud's thinking on the origin of paranoid thinking there is no evidence for a specific link between HS and pathological jealousy.

Obesity and sexual health

Obesity is associated with greater likelihood of erectile dysfunction. A French study (Bajos ea, 2010) found that obese women are less likely to have had a recent sex partner compared to women of normal weight but that obese people have similar sex practices and enjoy sex as much as other people do; obese women, more than obese men, are more likely to have an obese sex partner; and unplanned pregnancy and abortion are more likely among obese females because of reduced use of contraception. Goldbeck-Wood (2010) suggests that contraception data, focusing on the 'pill' and condoms, be treated cautiously and that long acting reversible contraceptives are suitable for obese women.

²⁰²⁹ Same-sex partnerships that are not recognised by law are associated with various difficulties: next-of-kinship, pensions, tenancy, inheritance tax, and illness in, institutionalisation of, or death of a partner.

²⁰³⁰ Spain allows gays to adopt and receive artificial insemination on same terms as heterosexuals.

²⁰³¹ According to the Irish Department of Health, 35% of deaths from AIDS up to July 1991 were among 'homosexuals/bisexuals' (H/Bs). This same group constituted 38% of known AIDS cases; there were 79 cases of AIDS among H/Bs, with 33 deaths, up to September of the same year, another 2 cases being recorded by late November. Seven of the latter were known IV drug users, with 6 deaths. However, a different source puts the figure for AIDS among HSs at 185 by that date; and another source still gives a minimum figure of 94 cases of H/B AIDS cases by the end of 1991! By the end of 1992, a year in which 38 Irish people died of AIDS, the rate of increase in HIV-infected cases was greatest in the heterosexual population. One fifth of HIV infected persons in 1994 were HSs, compared with 50% IV drug users and 13% heterosexuals. Twenty three percent of HIV cases notified in 1998 were HS. The breakdown of actual new cases of HIV in the following year was: total 209, drug misuse 69, heterosexual 59, HS 40, children 23, and prisoners 13.

In the US, up to the end of 1993 62% of males with AIDS got it from sex with other men, 2% of females received it from other women, and men infected 35% of women.

Parkinson's disease

Up to 60% of cases have arousal or orgasmic dysfunction. L-DOPA may increase sexual drive²⁰³² and improve erections. Increased sexual drive is common in patients treated with dopaminergic agents. Reduced levels of prolactin may play a role in such cases. A very few percent of patients on L-DOPA, especially males with early-onset paralysis agitans, become hypersexual and may masturbate excessively, indulge in sexual liaisons, and develop a wide variety of paraphilic tendencies. Management includes reduction in the dose of the offending drug and, if necessary, low a potency antipsychotic drug or anti-testosterone therapy.(Levy & Cummings, 2000)

Paraphilias²⁰³³

Sexual identity - personal feeling of maleness or femaleness

Gender identity - feeling that one is a man or a woman

Gender role - behaviours and attitudes considered appropriate for males and females in a given culture

Gender constancy - refers to the belief that ones sex is immutable - occurs at 5 to 6 years of age

Paraphilia - absence of a socially normative sexual object (the conservative object being the mature heterosexual partner) and aim (sexual intercourse, courtship, rearing a family, etc)

Exclusive paraphilia - deviant behaviour is essential for sexual satisfaction

Non-exclusive paraphilia - person is able to experience conventional as well as paraphiliac desires, although the latter are often preferred option

Intermittent paraphilia – the person only occasionally pursues paraphiliac needs (e.g. when under stress) or may have experienced paraphiliac needs during adolescent that later became dormant (e.g. during a satisfying sexual relationship) only to become overt again when under stress (e.g. break-up in a personal relationship)

Deviation - has many applications:

(a) unusual

(b) a symptom of an illness, physical or psychiatric

(c) behaviour is not acceptable to the society or subculture, e.g. immoral, illegal, etc

What behaviour is acceptable has varied with time and place throughout human history.(de Silva, 1999)

Not all sexual offences are driven by sexual desire. In such cases there is nothing to be gained from attempts at drive reduction.

Only the imagination limits what has been found to be sexually arousing, varying as it has from sneezing to the wind. Paraphilic behaviour is more common in males, although the number of females thought to be affected may be underestimated.(Agnew, 2001) No single personality profile would characterise any one paraphilia. Multiple paraphilias in the same person (polymorphous perversity) is a common finding. Paraphiliacs have achieved officially sanctioned positions looking after children, e.g. leader of a youth group. Not all paraphiliacs act out their fantasies or commit offenses. Few paraphiliacs look for help before an offence and the history is usually one measured in years before the person is arrested.

*Paedophilia*²⁰³⁴ (*vide supra*) is much commoner in males²⁰³⁵ and about 1% of homosexuals are paedophiles. Perhaps 60% of paedophiles are heterosexual, although figures given for different sexual orientations by different sources may add up more than 100%! Most give a history of CSA. Paedophilic behaviour may commence in the late years of life as a consequence of the disinhibiting effects of dementia. Psychopathy and brain damage (e.g. temporal lobe dysfunction) are common in the uncommon cases of paedophilic homicide. Most children seem to become involved with paedophiles because of fear, but a few may be promiscuous and delinquent. Contact may be made with minors via the internet. SSRIs and naltrexone are among the drugs reported to be helpful in some cases of paedophilia.

²⁰³² Sometimes this amounts to paraphilia.

²⁰³³ These were formerly known as sexual deviations/variations. 'Paraphilia' (*para*, beyond the usual; *philia*, love) was coined by Wilhem Stekel (1868-1940) in 1923. Stekel, an Austrian physician and psychologist and one-time disciple of Freud, died from suicide in London. Paraphilias in DSM-IV, disorders of sexual preference in ICD-10.

²⁰³⁴ *Child molestation* is broader than paedophilia: some paedophiles never act on fantasies and a person who never fantasises about minors might still have abused them.(Brotto & Klein, 2007, p. 540) Technically, paedophilia means sexual attraction to prepubescent children whereas *hebephilia* refers to sexual attraction to postpubescent children.

²⁰³⁵ But it is not exclusive to males.(Brotto & Klein, 2007, p. 541) It has been reported in association with Klinefelter syndrome.

Fetishism comes from the Portuguese for charm (*piquantism*, Fr. to arouse another's curiosity, infers the use of a fetish to facilitate sexual intercourse). Any living or inanimate object (e.g. soft or shiny materials, nappies, gloves) becomes necessary for successful sexual arousal. According to classic psychoanalytic theory, fetishism involves persistence of castration anxiety, anxiety being warded off by an uncommon belief that women possess a penis (therefore they won't want to cut off the man's penis)! There have been reports of an association with temporal lobe epilepsy. It has been rarely reported in women. (Brotto & Klein, 2007, p. 539) However, de Clérambault described 4 women who were arrested for stealing silk: they could only masturbate with stolen silk. (Draaisma²⁰³⁶, 2009, p. 264)

Necrophilia - sexual relations with the dead – may kill to obtain a corpse - schizophrenia, intellectual disability, and psychopathy common

Gerontophilia - sexual preference for elderly people - assault and rape may occur - young males are the usual perpetrators

Autogynaephilia – sexual arousal from notion of being equipped by physical attributes of both sexes; may look for hormones in order to achieve this state (e.g. a man wants breasts to go with his penis)

Apotemnophilia – sexually aroused by crippled people or amputees - much more common in males - may seek amputation or attempt it themselves²⁰³⁷ - *idée fixe* rather than a delusion – First (2005) draws parallels between amputation-seeking and gender identity disorder

Acrotomophobia – desire for sex with an amputee

Pygmalionism – use of sexual fetishes in human form

Partialism - focusing on one part of the body, such as the feet, to the exclusion of all else- aetiological theories usually based on learning theory (baby follows mother's feet leading to imprinting) or analytical philosophising.

Vogueing – dressing up as a celebrity to achieve arousal; *trashcanners* steal objects from dustbins of famous people for the same reason

While the use of actual fetish objects is more common among males, fetishistic fantasies are possibly equally distributed between the sexes. Treatment is either aimed at extinguishing the fetish (aversion therapy) or helping all parties concerned to adapt to harmless fetishes.

*Sadomasochism*²⁰³⁸: (a) *Sadism*²⁰³⁹. The sadist loves to make (consenting or non-consenting) others suffer. Sadists express their fantasies overtly. Consequences for the victim range from humiliation through beating to rape or death. Treatment is disappointing. (b) *Masochism*²⁰⁴⁰: The masochist wants to be humiliated²⁰⁴¹, this experience being necessary for orgasm. Behaviour therapy may have some effect. Reasons underlying the need to 'atone' require exploration. It is not uncommon to find both traits in the one person, with one predominating.

*Pornography*²⁰⁴² is strictly defined as obscene written descriptions used to induce sexual excitation although it can and does involve the other senses in practice. Sometimes a distinction is made between 'soft' (e.g. showing breasts) and 'hard' (e.g. showing genitalia) 'porn'. This may make as much sense as the same distinction between drugs of abuse. The relationship between pornography and sexual offences is controversial. Use of 900-number telephone sex lines in the USA, and similar facilities elsewhere, may lead to great financial indebtedness. This is only a paraphilia if there is a compulsive quality to it and if it is preferred to actual sex with a partner. Personality disorder and/or paraphilias may be overrepresented.

*Voyeurism*²⁰⁴³: The voyeur observes others involved in sexual activity, rarely harming anyone. Most are immature males who are afraid of real female contact. It may date from the viewing of parental sexual

²⁰³⁶ Draaisma (2009, p. 268) suggests that de Clérambault himself may have harboured similar fetishes!

²⁰³⁷ Apotemnophilia and amputee identity disorder do not necessarily co-exist in the same person.

²⁰³⁸ At least since Freud joined both terms it has been known that both 'poles' of this perversion are often linked; there is also a frequent association with fetishism and transvestic fetishism. What is included here is real sadism and masochism rather than simulated masochism.

²⁰³⁹ After the Marquis de Sade, a sadist, 1740-1814.

²⁰⁴⁰ After Sacher-Masoch, an Austrian novelist, 1836-95.

²⁰⁴¹ *Infantilism* refers to the wish to be treated as a baby, e.g. by wearing nappies. *Algolagnia* is the isolated love of pain.

²⁰⁴² 'The writings of harlots'. *Narratophilia* is the seeking of arousal from hearing sexual stories, *hybristophilia* is arousal sought from criminals, and *chrematistophilia* is arousal from being forced to pay for sex or from being robbed by the sex partner.

²⁰⁴³ Scopophilia or 'Peeping Tom'.

display during the voyeur's childhood. *Triolism* is the name given to the phenomenon whereby a man achieves sexual pleasure from watching his female partner having sex with another man. Voyeurism in women is rare, but this does not mean that think about or even peep!(Friday, 1975)

Transvestism: This is sexual arousal achieved by wearing hidden or visible (longstanding cases may feel confident enough to wear opposite sex attire publicly) female clothing. It can be normal and transient in adolescents. If persistent it becomes truly a fetish, i.e. it becomes essential before orgasm can be achieved. Masturbation is the usual accompaniment. Stealing clothes may lead to legal proceedings. Relapse may follow perceived rejection or other emotional stressors. Covert homosexuality may be present. Fenichel, the psychoanalyst, stated that the transvestite creates a 'phallic woman' of himself to allay fears of castration (cf. fetishism)! Aversion therapy has been used in the past. Clubs for transvestites have sprung up worldwide. Few people give up the practice completely despite any drawbacks they may encounter. Cross-dressing can be classified as follows. The *fetishistic transvestite*²⁰⁴⁴ is a male who wears female clothes as a fetish and masturbates while doing so; it is often associated with fetishism and masochism. The *transsexual* forms the second group.(*vide infra*) The double or dual role transvestite, usually male, spends part of his time as a heterosexual male and part dressed and passing as a female; unlike the transsexual, he has no desire for a permanent sex change. Lastly, the *homosexual transvestite*, who is of either sex, is attracted, of course, to members of the same sex. It is important not to assume that someone who engages in cross-dressing has something wrong with him. Some men, independent of sexual orientation, find the experience to be a calming one.(King, 2008, p. 703)

Sexual attraction to cross-dressed or anatomically feminised men is called *gynandromorphophilia*.

Stealing of used underwear from clothes lines is referred to as *snowdropping*.

*Transsexualism (gender identity disorder)*²⁰⁴⁵ was generally defined as involving the immutable belief, dating back to at least puberty, that the person is trapped in the body of the wrong sex. In fact, not every child with transsexualism retains this diagnosis into adulthood, although many boys who were transsexual as children will be homosexual or bisexual as adults. Many experts believe that gender identity disorder is part of a spectrum ranging from mild atypical gender behaviour through gender dysphoria to gender identity disorder. A collateral history is important to confirm the long-held belief of being trapped in a body of the wrong sex.

Primary - always considered himself as being female, even as a child; does see himself as homosexual; does not report homosexual fantasies; likely to cope well with surgical sex reassignment²⁰⁴⁶

Secondary - starts to feel that he is female at a later age, usually in adolescence²⁰⁴⁷; less likely to do well after surgery; described as essentially homosexual or transvestite

Transsexualism mimics – adolescence (a time of identity problems), effeminate homosexual males (transient wish for erotic reasons), borderline personality disorder (transient wish related to identity diffusion), and delusions (e.g. alien-induced incorrect genitalia)

Female children with the adrenogenital syndrome²⁰⁴⁸ may be boyish during childhood, but they do not become transsexual. Zhou ea (1995) found that the central subdivision of the bed nucleus of the stria terminalis in the hypothalamus was smaller in male-to-female transsexuals than in normal males and akin in size to normal females. The authors did not believe that this finding could be attributed to hormone therapy. Occasional cases of transsexualism following the onset of temporal lobe epilepsy have been reported and (generally uncontrolled) studies have reported an excess of EEG abnormalities in transsexuals. The transsexualism may disappear with anticonvulsant treatment.

²⁰⁴⁴ DSM-IV-TR limits this transvestic fetishism to males who are homosexual, which is patently not true.(Blanchard & Collins, 1993) Onset is very early in life. It was reported to occur at least once in 2.8% and 0.4% of Swedish males and females respectively.(Langstrom & Zucker, 2005)

²⁰⁴⁵ Gender identity disorder; eonism: Chevalier d'Eon de Beaumont, 18th century transsexual. Transsexual people, who naturally do not like the word 'disorder', prefer the term *transgender*. **Transgender Equality Network Ireland**, 085-1477166, www.teni.ie, info@teni.ie .

²⁰⁴⁶ Some non-transsexuals may seek sex reassignment, e.g. transvestites and effeminate homosexuals males.

²⁰⁴⁷ A small number of male cross-dressers may, after many years, cease to be excited by the activity and gradually become more certain that they are female.

²⁰⁴⁸ Excess androgen before and after birth.

Very rough estimates of prevalence for transsexualism are 1 per 30,000 adult males. The condition is very rare in adult females (1 per 100,000)²⁰⁴⁹. These figures refer to people seeking sex-reassignment surgery in the USA.(Becker & Johnson, 2003, p. 745) Transvestism and a desire for surgical re-sexing are integral components of the condition. It has been described in discordant MZ twins. Sex drive has been described as often being low and any sexual orientation is possible. Depression, substance abuse, personality disorder (borderline/dissocial/narcissistic²⁰⁵⁰), parasuicide, self-mutilation (often to force surgical intervention), and divorce are common. In one study, Dutch psychiatrists considered that gender identity disorder was an epiphenomenon of other psychiatric conditions (especially personality, mood, dissociative, and psychotic disorders) in 270 (75%) of 359 patients.(Campo ea, 2003) Female transsexuals are said to be more often homosexual than are their male counterparts. Rarely, chronic transvestism may change to transsexualism. If the patient can live as a woman for a certain number of years he can, in some countries, have a sex change (surgery and hormones). Over half of US States and most Western European countries allow birth certificate changes. In 2002, UK transsexuals received the right to marry a man or a woman and to have their gender changed on birth certificates²⁰⁵¹, whether or not sex reassignment surgery had been performed. A male-to-female transsexual was refused permission to change the name on the birth certificate in an Irish court in July 2002. In a case that divided medical opinion, a 13-year-old Australian girl was allowed hormone treatment as a possible prelude to later sex-change surgery. Some patients procure hormones via the internet or from abroad.(De Gascun ea, 2006) Many psychiatrists offer supportive psychotherapy only. Some patients view psychotherapy with suspicion, viewing it as a way of discouraging surgical intervention.(Becker & Johnson, 2003, p. 747) Patients can be determined to accept nothing short of surgery. Snaith (1987) reported that about 70% of patients are satisfied with the results of gender reassignment. Perhaps the strongest predictor of psychological problems following surgery is level of satisfaction with the results of surgery.(Barrett, 2008, p. 715) Some have sought surgical reversal to their former gender and others have committed post-reassignment suicide. Thorough evaluation and long-term support is required, and preliminary HIV testing has been advocated. Even in Britain, local services may be inadequate.(Murjan ea, 2002)

Female transsexuals require androgens (implant or IM injections). Oral androgens might be associated with increased risk of developing hepatocellular carcinoma. Surgical creation of a penis may fall short of expectations and such patients may need to accept non-penetrative sex.

Exhibitionism (flashing) is the commonest sexual deviation to involve legal proceedings²⁰⁵². About 20% appear in court on a second charge. A man (most often young, and can be married) exposes his penis, in any state of tumescence, to a female from a safe distance in lonely surroundings, and there is rarely any physical contact. He tries to shock her. Exhibitionism begins early in reproductive life and becomes most frequent when the perpetrator is under stress. The notion that such men are shy and immature has been undermined by research.(Brotto & Klein, 2007, p. 539) Cases that masturbate and shout at or touch the victim are more potentially dangerous than are those who simply expose themselves. Exposure to minors, a history of non-sexual crimes, a previous conviction for exhibitionism, and exposure of an erect penis suggests recidivism. Management has included aversion therapy (e.g. imagining the scene and dreadful consequences), group therapy (spousal involvement when feasible), and drugs. Rarely one comes across women who repeatedly expose their breasts, and very rarely one sees women who do the same with their genitalia.(Federoff ea, 1999) However, according to Blair and Lanyon,(1981) female exhibitionistic behaviour is usually performed for monetary gain rather than for any sexual pleasure experienced on their part.

Coprophagia - eating of faeces, as the preferred method of achieving sexual arousal; may be part of a masochistic ritual; masochist may have to lick the sadist clean; coprophagia and *coprophilia*, the storing of faeces²⁰⁵³ are usually associated with intellectual disability, the degenerative psychoses of childhood, and

²⁰⁴⁹ The De Gascun ea(2006) Dublin series consisted of 52 cases, 45 male to female, and 7 female to male.

²⁰⁵⁰ This is not necessarily an aetiological relationship.(e.g. Fossati ea, 1999)

²⁰⁵¹ The *Gender Recognition Act* requires backing of two doctors, one a specialist and the other usually the GP. The applicant must have lived in their assumed gender role for at least 2 years. Application is made to the Gender Recognition Panel in Leicester (www.grp.gov.uk). Of course, their birth certificate must be a UK one.

²⁰⁵² It does not include homosexual courting.

²⁰⁵³ Sometimes defined as thinking about or observing defecation.

schizophrenia; term coprophilia may also refer to the deriving of sexual pleasure from watching the act of defecation; these terms should not be confused with coprolalia (utterance of obscenities as in schizophrenia or Tourette syndrome)

Infundibulation (stigmatophilia) – making holes, piercing or inserting rings²⁰⁵⁴ in the skin

Partial asphyxia (hypoxyphilia, asphyxiophilia) - man dons feminine attire and suspends himself on stairway while masturbating; plastic bag may be placed over head; rope may be suspended around neck to alter consciousness; may meet their death this way by accident

Urophilia (undinism²⁰⁵⁵) - aroused by watching the act of urination, by being urinated upon (*golden shower* or *urolognia*), by urinating during sexual intercourse, or by drinking urine

Sexual urethrisism - usually a woman who is aroused by urethral stimulation; *urethralism* involves pleasure in inserting objects into the urethra, e.g. catheters (*catheterophilia*)

Klismania or *klismaphilia* - use of enemas as sole or chief source of sexual pleasure

Mysophilia - sexual arousal by filth or smelly, soiled clothes

Telephone scatalogia - obscene phone calls replace orthodox sexual outlets

Frotteurism²⁰⁵⁶ (Fr. to rub) - man rubs up against unsuspecting female,²⁰⁵⁷ often on crowded public transport; usually fantasises about an exclusive, caring relationship with the female; said to be associated with Asperger's syndrome

Bestiality (Zoophilia) - sexual preference for intercourse with animals; stereotype is young, mentally subnormal shepherd; in *formicophilia* there is a preference for small creatures touching the genitalia

Sodomy (anal intercourse) – in medicine buggery²⁰⁵⁸ is synonymous with sodomy²⁰⁵⁹ but legally it refers to either sodomy or bestiality; an increase in the number of men practising anal sex in England was reported in 1991

Pederasty (paederasty) - anal intercourse practiced by adults with boys

Oralism - focusing on oro-genital contact to the exclusion of sexual intercourse

Management: It is insufficient to aim at removing the sexual variation/paraphilia. Conventional outlets should be boosted, e.g. *orgasmic reconditioning* (think of paraphilic behaviour whilst masturbating but switch to a more acceptable fantasy when orgasm becomes inevitable) and *covert sensitisation* (fantasise about the paraphilic behaviour but add a noxious element, such as imagining being caught or having diarrhoea), although the effectiveness of such approaches is unclear. In some cases it may be pragmatic to make a fetish more acceptable to a partner, e.g. by settling for the wearing of a leather armband instead of full leather gear.

Cognitive-behavioural approaches are useful. Group therapy, the effects of which are modest, aims include accepting responsibility, empathising with the victim, and nourishing true motivation for change/controlling behaviour. The aim is to reduce recidivism rather than cure.

Drugs used for excessive (uncontrolled, dangerous) sexual drive: These drugs may be best for paraphilia patients with a high sex drive rather than for antisocial paraphiliacs with a low sex drive. (Cooper, 1986) In one meta-analysis (Hanson and Morton-Bourgon, 2005), the best predictors of recidivism were sexual deviation and antisocial tendencies. Hormones do not guarantee absence of recidivism and they are not a stand-alone therapy. It is important that patients accept responsibility for their actions and that they become involved in psychotherapy. Luteinising hormone (LH) controls testicular androgen secretion. Progestogens inhibit LH secretion from the pituitary. Anti-androgens like cyproterone and medroxyprogesterone act to decrease testosterone levels and to block its receptors. Cyproterone (or ciproterone) acetate²⁰⁶⁰ (Androcur) is a synthetic, progesterone-like antiandrogen that caused a decrease in serum testosterone, LH and FSH levels and a rise in serum prolactin. It is a competitive inhibitor of testosterone and dihydrotestosterone at androgen receptors. 50 mgs b.i.d. p.o. is a reasonable average dose. It may cause a reversible atrophy of the

²⁰⁵⁴ An example would be a Prince Albert ring piercing the penis.

²⁰⁵⁵ Gk: water spirit.

²⁰⁵⁶ Also called frottage; if the hands are used to touch the other person the term *toucherism* (e.g. surreptitious touching or rubbing of another's genitals) has been applied.

²⁰⁵⁷ Frotteurism is excessively rare in females. (Federoff et al, 1999)

²⁰⁵⁸ This term arises from the Bosnian Bogomils, a tenth century heretical sect (e.g. God had 2 sons) that was said to practice sodomy.

²⁰⁵⁹ Called after Sodom (*Genesis* 18-20), the city of evil.

²⁰⁶⁰ This was synthesised in Germany by Wiechert, 1961.

seminiferous tubules or liver damage (check LFTs) and can also cause gynaecomastia (up to 20%, sometimes irreversible), sedation, tiredness, and depression. Cyproterone reduces sexual interest and activity but does not impair the erectile response to erotic films. Not all patients lose desire for sex or erections despite being on relatively high doses. There is oligospermia and loss of ejaculation. Cyproterone is considered to be most effective when the paedophile is focused on orgasm and to be less effective when the patient is more focused on forming a relationship with the victim. Cyproterone should not be given without an oestrogen (e.g. ethinyl oestradiol) to a woman during reproductive life because, if she became pregnant, there might be sex differentiation problems in the male foetus. Cyproterone acetate is found in low dosage in the contraceptive pills Dianette and Minerva²⁰⁶¹, which has been used in women who suffer from severe acne. The effects of cyproterone may take some months to disappear. Some patients show habituation to the drug and need a dosage increase.

Oestrogens can be given as depot injections (oestradiol undeclyenate) or as an oestradiol implant. Oestrogens can cause breast enlargement and nodules, testicular atrophy, osteoporosis and, rarely, breast tumours. Medroxyprogesterone²⁰⁶² (Depo-Provera), a progestagen that induces hepatic testosterone reductase, was given IM before being taken off the market in 2003; it had many other uses, e.g. certain hormone-sensitive malignancies, endometriosis, and infertility. Goserelin (Zoladex), a long acting LH analogue, is given s.c. It is used for endometriosis, prostatic cancer, premenopausal breast cancer, and as an adjunct to surgery for uterine fibroids. A single injection reduces LH and testosterone levels for a month. It reduces sex drive. It can cause hot flushes, loss of libido, headaches, mood changes, and vaginal dryness²⁰⁶³. Triptorelin (Decapeptyl, Gonapeptyl depot) is a long-acting GnRH agonist that reduces testosterone levels that also seems effective. It can cause erectile failure, hot flushes, and reduced bone density in some men. Leuprolide²⁰⁶⁴ (aka leuprorelin) acetate (Eligard, Prostep), another LH agonist, is preferred to medroxyprogesterone or cyproterone by many therapists because it causes a greater fall in testosterone levels; also, being a peptide, it is safer than steroids.

Physical castration, a thorny ethical issue (Grubin & Beech, 2010), was practised as a voluntary treatment for sexual perversities on rare occasions in some countries, such as in Denmark until 1972. However, it is still carried out in psychiatric hospitals for sexual offending in the Czech Republic. It was introduced in California for convicted paedophiles in 1996.(Macready, 1996) Castration can reduce sex drive but some people persist in seeking sexual activity and may even achieve penile tumescence and a third can achieve sexual intercourse. Also, androgens are also produced by the adrenal glands. The present author has found records of one intellectually disabled female who received a leucotomy in early twentieth century Ireland for what was deemed to be promiscuous behaviour. Ablation of the temporal lobe has been used in Eastern Europe for paraphilias. People may agree to be castrated in order to gain release from confinement rather than because they truly wish to reduce the risk posed to others.

Preoccupation with castration (DSM-IV): Such persons, of either sex, are preoccupied with castration or penectomy. They do not wish to acquire the secondary sexual characteristics of the opposite sex but are uncomfortable with their assigned sex (contrast with transsexualism). They fantasise about being of a different gender, and are often asexual.

Aversion therapy consisted of the pairing of a noxious stimulus (agents such as ammonia, apomorphine, disulfiram, nalorphine, or emetine; electric shocks) with the response/behaviour to be weakened or extinguished (alcohol, morphine, pictures of men and women, etc). The results of aversion therapy for paraphilia were often transient. Also, patients often became socially isolated and depressed because of the lack of an alternative sexual outlet.

Entry of sexual offenders onto a *sexual offenders' register* has different implications in different jurisdictions. They may be required to live at a particular address, report at stated frequencies to police, avoid minors or schools, or wear an electronic tag. Horrific sex crimes during the 1980s in the US led a number of states (beginning with Washington in 1990) to enact laws leading to civil commitment after the

²⁰⁶¹ Do not use if there is a history of venous thromboembolism.

²⁰⁶² Medroxyprogesterone induces hepatic testosterone A reductase and thereby lowers plasma testosterone.

²⁰⁶³ Antihistaminic or anticholinergic drugs can cause vaginal dryness.

²⁰⁶⁴ Leuprolide acetate is usually used for hormone dependent advanced prostate cancer. Side effects include testicular atrophy and pain, infertility, breast tenderness, fatigue, hot flushes and night sweats, skin problems, myalgia, prolonged coagulation time/ecchymoses, increased CPK levels, and rigors. FSH and LH secretion is initially increased followed by a decrease because of downregulation of receptors.

predator finished his prison term. This could mean indefinite confinement in a specialised treatment facility. Such measures were held to be constitutional by the Supreme Court, although the APA (1999) was not happy with such statutes.

Sexual Dysfunction

Sexual problems are more often transient than persistent. Problems of sexual desire and interest often carry a poor prognosis, although one should realise that some people who are locked in a relationship in which they have no say develop lack of desire as a form of protest. (Ritvo ea, 2008, p. 1318) Problems of self-esteem (try individual counselling or cognitive therapy) and interpersonal problems are common. Sexual dysfunction occurs in at least 10% of psychiatric outpatients. Osborn ea (1988) reported that one-third of women aged 35-39 had operationally defined sexual dysfunction in a community survey in Oxford, especially impaired sexual interest, vaginal dryness, infrequent orgasm, and dyspareunia. These were significantly associated with increasing age, psychiatric disorder, neuroticism, and marital disharmony. Rust ea (1988) found that marital problems were more closely related to sexual dysfunction in men than in women.

*Classifying marital distress (MD) and sexual problems (SPs)*²⁰⁶⁵

SPs causes/adds to MD

MD causes/adds SPs

MD + SPs co-occur

SPs without MD

MD without SPs

'Spectatoring' refers to the habit of monitoring and observing ones own love making rather than simply participating. This can lead to a vicious circle of performance anxiety and dysfunction. Men's performance oriented approach to sex is inappropriate when applied to sexual intimacy. (Bignell, 1993)

'PLISSIT' refers to four steps (depending on the situation) in treatment: (P) permission giving, (LI) limited information, (SS) specific suggestion, and (IT) intensive treatment. The first three (PLISS) make up brief therapy. They are less applicable in practice as one moves from P to IT.

The concept of the 'core complex' can be mentioned here in passing. The person is torn between love and hate for the partner, between a need for closeness and a wish for escape. According to the theory, the person's mother had maintained her child in an excessively dependent state, causing the child to feel threatened, frustrated and aggressive toward the mother, but at the same time wanting her love and protection. He therefore represses his anger. The conflict is re-experienced in adult sexual relationships as a wish for proximity accompanied by fears of being overpowered.

The physical examination of a patient with sexual problems is discussed by Dean. (1998) Examples of what to look out for in males include the firm penile plaques of Peyronie's disease and the tender prostate in prostatitis²⁰⁶⁶. The woman should be examined while her bladder is full since detrusor instability may be associated with voiding during intercourse. Chlamydiosis is one cause of dyspareunia. Bacterial and chlamydial swabs may be taken from the vagina and the endocervical canal. In the case of both sexes, the examiner should consider cultural mores and offer a chaperone.

Sexual dysfunction is extremely common in schizophrenia. Macdonald ea (2003) found that 82% of males (low desire, erection difficulties, premature ejaculation, and low intensity ejaculation) and 96% of females (low enjoyment) reported at least one sexual dysfunction. Sexual dysfunction in females was associated with negative schizophrenic symptoms and general psychopathology. Interestingly, the authors found no association between sexual dysfunction and the type of antipsychotic drug being taken. However, it was impossible to separate illness from medication effects since most patients were taking medication and few patients relative to controls had a partner.

*Hypoactive desire disorder*²⁰⁶⁷ (*sexual desire disorder*) refers to lack or loss of sexual desire. It is much common in females than in males. It often reflects relationship problems²⁰⁶⁸, daily hassles, and high stress

²⁰⁶⁵ Modified from Ritvo ea (2008, pp. 1318-9).

²⁰⁶⁶ Prostatitis may cause perineal pain, painful ejaculation, or altered sensation.

²⁰⁶⁷ Some authors suggest combining desire and arousal disorders under the heading 'sexual arousability disorder'.

²⁰⁶⁸ E.g. loss of attraction due to obesity, dull sexual routines, too much or too little closeness, religious concerns, power issues.

jobs. Rearing children may encroach on 'couple time'. Occasionally there is a specific sexual problem due to longterm sexual inhibition or an intractable biologically based low sex drive. It may be secondary to depression,²⁰⁶⁹ but it doesn't always clear up when the depression is treated. OCD may interfere with sexual desire. (Meston & Frohlich, 2002) Gregoire (1999a) states that up to 10% of men presenting with inhibited sexual desire may have a prolactin secreting pituitary tumour! Ginseng²⁰⁷⁰ is an ancient oriental aphrodisiac and tonic. Tibolone²⁰⁷¹ (Livial) may enhance sexual function in post-menopausal women, (King, 2008, p. 701) although more evidence is needed. Flibanserin, originally developed as an antidepressant, is undergoing trials with some promise of success. The FDA in America approved EROS-CTD²⁰⁷² in 2000, a small vacuum pump that applies gentle suction to the clitoris in order to increase its blood supply and increase desire. In '*sexual aversion disorder*' the person hates genital contact; it is severe and persistent; and the causes may be the same or similar to hypoactive desire disorder. '*Sexual phobia*' is rare. There is avoidance of sexual experience because of a specific anxiety that is seen as excessive by the patient. The anxiety may be confined to an aspect of sexual activity (kissing, smells, nudity, etc) or it may be generalised.

Sexual compulsion/addiction is not found in the DSM but does exist. One partner constantly seeks sexual activity and becomes distressed if such desires are not fulfilled. Some people who engage in extramarital affairs have this problem. Various therapeutic approaches have been advocated (Ritvo ea, 2008, p. 1319): 12-step approach (modelled on Alcoholics Anonymous), group therapy, couple therapy (even if it involves helping to negotiate an ending to the relationship), and SSRIs.

Males

Premature ejaculation is especially found in younger men. An older definition was that on at least 50% of occasions the male is unable to delay orgasm long enough to satisfy the female. DSM-IV, in paraphrased form, states that the man ejaculates too quickly, before he wishes it. It is often learned from earlier experiences but organic causes include testosterone deficiency, prostatitis, and multiple sclerosis. Treatments include the squeeze technique, withdrawal of stimulation just before the build up to orgasm (*stop-go technique*²⁰⁷³), and the application of a local anaesthetic ointment to the coronal ridge and frenulum to reduce stimulation. In the *squeeze method* the woman grips the corona glandis for a few seconds between her thumb and forefinger and then releases it suddenly. This technique may lead to loss of erection or even of ejaculation when employed too close to the point of ejaculatory inevitability. SSRIs cause the opposite effect, delayed ejaculation, and therefore may be useful in depressed males with concomitant premature ejaculation, whereas nefazodone (Dutonin – no longer available) is unhelpful in this scenario. Mirtazapine may attenuate nausea and sexual dysfunction due to SSRIs. Low dose BZDs, TCAs (clomipramine 50 mgs), SSRIs, and thioridazine may be beneficial when taken an hour or so before sexual intercourse. Spontaneous ejaculation has been described in a patient receiving reboxetine. Dapoxetine, a short acting SSRI (30-60 mg; max. serum conc. c. 1 hr.; initial half-life 1.2 hr.; 24 hr. plasma conc. < 5% peak value) is taken 1-3 hours before sex and has been shown to be effective. (Pryor ea, 2006) Adverse effects include nausea, diarrhoea, headache, and dizziness. A particular problem associated with use of clomipramine and the SSRIs is that they may reduce desire to have sex! A topical lidocaine-prilocaine solution helps some sufferers as long as anaesthesia is not extreme and there is no allergic skin reaction. *Delayed ejaculation (ejaculatory incompetence or retarded ejaculation)* refers to a long delay in, or inability, to ejaculate. This is usually psychogenic if the patient is able to ejaculate outside the vagina. It may be due to fear of creating a pregnancy, negative feelings for the partner, religious taboo, etc. Physical

²⁰⁶⁹ Also, increased sexual interest is reported by a minority of people with depressive or anxiety states and many individuals with these disorders find no change in their interest in sex. Sex may act as a transient anxiolytic or as a source of comforting closeness for some people.

²⁰⁷⁰ **Ginseng** from *Panax* (Gk: panacea) *ginseng* contains terpenes and saponins and has antioxidant properties. It has oestrogenic (may cause vaginal bleeding and breast pain) and hypoglycaemic effects (affects on liver lipogenesis and storage of glycogen) and blocks reuptake of 5-HT, DA, noradrenaline and glutamate. It blocks production of thromboxane A2 and thereby inhibits aggregation of platelets (which can be problematic in people on warfarin). Other adverse effects include headache, anxiety, poor concentration, raised blood pressure, palpitations, and diarrhoea. (see Dunne, 2009)

²⁰⁷¹ Synthetic steroid that is oestrogenic, androgenic and progestogenic; used to treat menopausal symptoms. It has a number of adverse effects including thrombophlebitis, hypertension, and vaginal bleeding.

²⁰⁷² Clitoral therapy device.

²⁰⁷³ Described by J. Semans in 1956.

factors (drugs such as antidepressants, deficiency of androgens, etc) are less likely to be so situation-specific. Neurological disease (e.g. spinal cord lesions or prostatectomy²⁰⁷⁴) and drugs such as alpha-adrenergic blocking agents may lead to 'dry run' orgasm (i.e. orgasm occurs but semen blocked during passage) or retrograde ejaculation ('dry orgasm' - semen enters urinary bladder – sperm in post-ejaculatory urine – infertility units may centrifuge urine and collect sperm²⁰⁷⁵). Treatment involves masturbation of the male by the female externally. Eventually she places the penis in the vagina at the appropriate moment. This usually breaks the vicious circle in psychogenic cases. The female should kneel over the male. It should be noted that normal aged males often produce an ejaculate only every second or third time. Intermittent use²⁰⁷⁶ of SSRIs, e.g. sertraline 50 mgs, has been recommended.

In diabetics, neuropathic involvement of the bladder neck may lead to retrograde ejaculation (cloudy urine). Ephedrine taken prior to sexual intercourse has been recommended but this can be dangerous, especially if combined with caffeine.

A morning or non-coital erection does not outrule orgasmic dysfunction. For example, people on beta-blockers or MAOIs may have drug-induced orgasmic dysfunction despite normal morning erections. (Fagan & Schmidt, 2000)

Painful ejaculation is a rare, often idiopathic disorder. There may be an inflammatory condition, such as urethritis or prostatitis.

Erectile dysfunction/disorder (ED, impotence; O'Shea ea, 2001) is an inability to achieve or maintain penile erection until completion of sexual activity, affects about 7.5% of males (average of three studies). *ICD-10* tends to stress satisfaction and enjoyment in sexual relationships in its definition, whereas *DSM-IV* takes a more physiological approach²⁰⁷⁷. Diagnosis is based on a thorough history, including collateral information as necessary, and examination, supplemented by whatever investigations seem indicated and sensible. The *International Index of Erectile Function*, a validated questionnaire, has 5 domains: erectile function, orgasmic function, sexual desire, satisfaction with sexual intercourse, and overall sexual satisfaction.

Relevant physiology

Erotic stimulation may require activation of caudal thalamic intralaminar nuclei

Parasympathetic stimulation of erection does not seem to work directly via acetylcholine

Various chemicals are involved in causing penile smooth muscle relaxation: nitric oxide²⁰⁷⁸, vasoactive intestinal polypeptide (VIP), and prostaglandin

Cyproterone acetate reduces sexual interest and activity, but not erectile response to erotic pictures; the same phenomenon is seen with other causes of hypogonadism: *therefore androgens are not essential for erection*

Vomer nasal or Jacobsen's organ of the nasopharyngeal septum secretes volatile chemicals called *pheromones* or *copulins*, and is linked to the olfactory system and hypothalamus, leading, when stimulated, to gonadotrophin release and, it is contended, to sexual arousal

Canine bitches secrete urinary substances at oestrus which stimulate the male to produce luteinizing hormone and testosterone

Certain genetic mutations that affect resting endothelial function carry an increased risk of developing ED, e.g. polymorphisms of the genes for nitric oxide synthase and Rho kinase

Whatever the primitive biological underpinnings, it is important to note that sexual arousal and potency have obvious perceptual and cognitive components in humans. A cross-section of the erect penile shaft, relative to the flaccid penis, reveals engorged veins, narrowed cavernous²⁰⁷⁹ and Helicine²⁰⁸⁰ arteries, and bloated sinusoidal spaces.

²⁰⁷⁴ Transurethral prostatectomy (TUR) may reduce orgasmic sensation and cause retrograde ejaculation. Radical pelvic, including prostatectomy, for cancer can impair erectile function. Erectile dysfunction is uncommon after TUR.

²⁰⁷⁵ 74 days are required for spermatogenesis. Therefore today's sperm reflect the man's health that many days ago.

²⁰⁷⁶ Less nausea and reduced libido.

²⁰⁷⁷ DSM-IV, as with all disorders, stresses the fact that ED causes marked distress or interpersonal difficulty.

²⁰⁷⁸ Also produced in the clitoris.

²⁰⁷⁹ In centre of corpus cavernosum.

Types of penile erection requirements, and effects of spinal cord trauma

reflex erections – not caused by thinking/seeing erotica

- results from penile stimulation
- requires S2-S4 nerve roots: sacral reflex arc
- mediated by parasympathetic fibres
- usually present with injury above L2 vertebra

psychogenic erections – caused by thinking/seeing erotica

- mediated by sympathetic fibres
- not caused by direct stimulation of penis
- thoracolumbar roots essential
- often lost with thoracic or cervical cord injury

Aetiology of erectile impotence

Drugs: alcohol²⁰⁸¹, tobacco²⁰⁸², lithium, antidepressants²⁰⁸³, antipsychotic drugs²⁰⁸⁴, barbiturates, benzodiazepines, opiates (may be reversed in some cases with naltrexone), psychostimulants²⁰⁸⁵, cannabis, anti-androgens, methotrexate, anticholinergic drugs²⁰⁸⁶, H2-blockers²⁰⁸⁷, antihypertensives (chiefly if centrally acting, such as guanethidine and alpha-methyl dopa²⁰⁸⁸), digoxin, clofibrate, gemfibrozil, thiazides, spironolactone, interferon- α

*Physical*²⁰⁸⁹: multiple sclerosis, Parkinson's disease²⁰⁹⁰, Addison's disease, diabetes mellitus, hypo- or hyperthyroidism, acromegaly, temporal lobe epilepsy, syphilis, pituitary adenoma, peripheral vascular disease²⁰⁹¹, pelvic surgery (e.g. prostate) or irradiation, spinal cord trauma, bicycle riding²⁰⁹², Klinefelter's syndrome, hepatic cirrhosis, cardiac disease, chronic renal failure²⁰⁹³, malnutrition, etc

Psychological/psychiatric: anxiety, depression, organic brain syndromes, schizophrenia, etc

Causes of ED have been divided into the largely psychological²⁰⁹⁴, largely physical, or combined psychophysical. Older men are especially vulnerable. ED can be primary or secondary (former if an erection never achieved, latter if function is lost). The majority of cases are secondary. ED can be partner-specific. Fear, guilt, and drugs²⁰⁹⁵ are common causes of ED and alcohol is a testicular toxin. Diabetes mellitus (DM) causes erectile problems, especially in older men, probably via a combination of neuropathy

²⁰⁸⁰ Branches from cavernous artery to sinusoidal spaces.

²⁰⁸¹ The acute effects of alcohol ('brewer's droop') are well known. The chronic alcoholic with hepatic dysfunction may have hypogonadism, feminisation, and peripheral neuropathy.

²⁰⁸² Nicotine decreases blood flow in the corpus cavernosum and inhibits cavernosal venoconstriction.

²⁰⁸³ SSRIs, TCAs, and MAOIs.

²⁰⁸⁴ This is dose related: low doses of antipsychotic drugs facilitate erection, high doses impair erection. It also responds to sildenafil. (Gopalakrishnan ea, 2006)

²⁰⁸⁵ Cocaine.

²⁰⁸⁶ Disopyramide and anticonvulsants.

²⁰⁸⁷ Ranitidine, cimetidine.

²⁰⁸⁸ Also calcium-channel blockers, clonidine, reserpine, and beta-blockers; angiotensin II receptor blockers such as losartan (Cozaar) are said to be free of sexual side effects. Antihypertensives, by lowering systemic blood pressure, can reduce maximal penile filling capacity.

²⁰⁸⁹ See Rees ea (2007) and McVary (2007) for details.

²⁰⁹⁰ L-DOPA may facilitate erection.

²⁰⁹¹ The bore of the penile artery is tiny and any reduction in arterial diameter may lead to ED long before other cardiac symptoms (e.g. angina) occur.

²⁰⁹² This may damage the perineal nerve causing numbness of the penis and it may cause ED by reducing oxygen pressure in the pudendal arteries.

²⁰⁹³ Uraemia is accompanied by increased LH, oestrogen and prolactin and decreased testosterone levels. Erythropoietin may improve sexual function, probably by reversing some of these hormonal changes.

²⁰⁹⁴ This has been criticised as being overly simplistic since anxiety can also increase male and female sexual arousal. Is anxiety a problem only for those who already have a dysfunction? (King, 2008, p. 698)

²⁰⁹⁵ E.g. thioridazine, beta-blockers, nicotine, and alcohol ('brewer's droop').

and arteriopathy. Psychogenic factors may be the chief cause in many cases of DM. Diabetic women may have decreased sexual arousal, poor vaginal lubrication, reduced orgasmic capacity, or depression. Peyronie's disease²⁰⁹⁶ causes different degrees of deformity of the erect penis. Leriche's syndrome²⁰⁹⁷ and small vessel disorders²⁰⁹⁸ are other causes.

The search for physical causes of ED cannot replace a holistic, multidisciplinary approach to what is a complex problem. A thorough physical examination is essential. Cultural mores must be respected, and a chaperone has become essential in the current litigious climate. Physical investigation of the aetiology of erectile dysfunction has become less imperative with the introduction of effective oral treatments. Measurement of penile arterial blood pressure involves a Doppler probe, a digital blood pressure cuff, and a sphygmomanometer. Nocturnal penile tumescence²⁰⁹⁹ can be monitored, but its usefulness in distinguishing between psychological and organic causes of ED may have been exaggerated. Cavemosography, wherein a contrast medium is infused to examine the corpora cavernosa and their drainage, can help to identify leaks. Pelvic arteriography is used to demonstrate arterial obstruction. Conduction latency in the dorsal nerve and bulbocavernous reflex latency are other tests that may be relevant.

Psychological treatment is usually a modification of the Masters and Johnson technique, although it has not proved possible to replicate the original high cure rates. Patients with organic impotence may be encouraged to explore other forms of sexual activity with their partners. Individual and interpersonal dynamic factors should not be ignored: for example, there is no point in focusing on sex in a relationship that is unhappy for other reasons. Individual, marital, couple or family approaches may be warranted in complex cases; separate attention to substance use disorders may be indicated. A problem may arise because the partner is not interested in seeking help.(King, 2008, p. 698)

Kegel's pelvic floor exercises are often prescribed for ED (or premature ejaculation) but there is only a little evidence that they are effective.(King, 2008, p. 699)

Testosterone has little effect on erectile dysfunction and is more important in sustaining sexual drive and the capacity for ejaculation. However, low sexual drive secondary to hypogonadism (older men with hypogonadism may suffer an excess of depression: Shores ea, 2004) would be an indication for employing this hormone. Low testosterone levels are treated with a series of depot testosterone injections.

Gonadotropin-releasing hormone²¹⁰⁰ can be used when hypogonadism is secondary to hypothalamic or pituitary disorders. Bromocriptine is indicated for those rare cases of hyperprolactinaemia (prolactin inhibits central dopaminergic activity and so reduces gonadotrophic hormone-releasing hormone secretion) due to idiopathic causes or secondary to pituitary adenoma. Yohimbine²¹⁰¹, an alpha-adrenoreceptor blocker, has been used especially in psychogenic cases. One group achieved a 38% success rate for situational ED. Topical nitroglycerine may produce a useful erection in some men; headache in the partner due to transvaginal absorption may be avoided by using a condom. One study found that topical creams²¹⁰² were best in psychogenic ED. However, topical preparations are generally not as successful as injections. Trazodone, which causes priapism²¹⁰³ in 1 in 6,000 treated males, has been used for (especially psychogenic) ED.(Fink ea, 2003) Various strategies employed to reduce the sexual side-effects of antidepressants include dose reduction, weekend drug holidays for short half-life agents, change of drug²¹⁰⁴, taking the drug after coitus, and various chemicals: cyproheptadine, bethanacol, amantadine, yohimbine, buspirone (withdrawn 2009), and bupropion. Some workers are not convinced that oral medications like yohimbine have efficacy (but see PDE5 inhibitors).

²⁰⁹⁶ Idiopathic fibrosis of corpus cavernosum with firm plaques.

²⁰⁹⁷ Large vessel obstruction.

²⁰⁹⁸ Obstruction of internal pudendal arteries or of the penile arteries in older men; arterial inadequacy or 'dysplasia' in primary cases; and venous incompetence where too much blood is lost by the penis to the general circulation.

²⁰⁹⁹ **Nocturnal penile tumescence** occurs during REM sleep. We know that it is androgen dependent. It is postulated that the brain normally inhibits erection via noradrenergic nerve cells in the locus coeruleus and that such descending inhibitory tone is turned off during REM sleep.

²¹⁰⁰ GnRH, luteinizing hormone-releasing hormone, LHRH, a decapeptide.

²¹⁰¹ Indole alkaloid found in many plants (e.g. root of *Rauwolfia* and bark of African *Pausinystalia yohimbe* tree). It can cause anxiety, headache, nausea, and hypertension.

²¹⁰² Combinations of aminophylline, isosorbide dinitrate, and co-dergocrine mesylate.

²¹⁰³ Priapus is seen weighing his huge penis in a fresco in the Villa dei Vetii, Pompeii, first century.

²¹⁰⁴ E.g. an SSRI to mirtazapine.(Gelenberg ea, 2000)

Advertisements for sildenafil (see below) and other similar drugs on the internet are ubiquitous and the products being sold may contain too little or too much of the active ingredient. They may also contain potentially toxic metals.

Phosphodiesterase type-5 (PDE5) inhibitors, which cause nitric oxide release, include sildenafil, tadalafil, and vardenafil. These are all taken orally. Sexual stimulation is required for these drugs to produce an erection because in the absence of sexual stimulation concentrations of nitric oxide and cyclic GMP are low. Sildenafil (Viagra; a PDE5 inhibitor): The usual starting dose is 50 mgs one hour before sex. The dose can be changed as needed: range, 25-100 mgs. It should only be used once daily. Side effects include painful erection (>17% of males), headache, dizziness, flushing, sweating, dyspepsia, nasal congestion, and a bluish tinge to vision (limited inhibition of phosphodiesterase type 6 in the retina), increased light perception or blurred vision. Driving may be a problem. Muscle aches follow frequent use. The incidence of priapism ranges from 0.35-4% (a similar problem with the female clitoris is possible), and fibrosis occurs in 1-23% of users. It may be abused alone or with 'ecstasy' (MDMA), the combination being called 'sextasy'. Abuse may lead to priapism with resultant sexual dysfunction! Mixing PDE5 inhibitors with drugs containing nitric oxide (e.g. "poppers", which contain amyl nitrate) can cause hypotension, with the potential for myocardial infarction or stroke²¹⁰⁵. Failure of sildenafil may lead to distress and exacerbation of low self esteem. (Tomlinson & Wright, 2004) Interestingly, the lotus flower²¹⁰⁶ contains, among other things, phosphodiesterase inhibitors: it was often sniffed or taken in wine!

Sildenafil citrate (Viagra)

Effective across full range of aetiologies²¹⁰⁷ (incl. serotonergic antidepressant-induced dysfunction) – overall effectiveness is 50% of cases; may reverse gastroparesis in diabetes

Increases hypotensive effect of nitrates: avoid amyl nitrite or any nitrates (sildenafil is used for pulmonary arterial hypertension)

Metabolism: P450 isoforms: mainly 3A4, less so by 2C9; inhibitors of these enzymes reduce clearance

Highly protein bound: dialysis unhelpful after overdose

Avoid if: severe hepatic impairment, BP <90/50, recent CVA or MI, known family history of degenerative retinal disorders²¹⁰⁸

Caution in: abnormal penis²¹⁰⁹ or risk of priapism²¹¹⁰ or concurrent use of dihydrocodeine²¹¹¹

Does not increase arousal in females (Basson ea, 2002)

Adverse effects of intracavernosal vasoactive injection

Mild, non-specific changes in liver function tests

Haematoma, bruising

Fibrosis, nodules

Priapism: necrosis if persistent

Local pain

Dizziness and faints: psychogenic?

Death if papaveratum used in error instead of papaverine

Abuse of, at sex shows

²¹⁰⁵ **Should a person who has taken a PDE5 inhibitor require medical attention (e.g. in an emergency department) the doctor should be advised of medication taken lest nitrates are administered!** There is concern over the sale of so-called 'herbal Viagra' products that may contain large amounts of PDE5 inhibitors such as sildenafil and tadalafil. Sibutramine, an MAOI, has also been found in such products. Internet sales of such products should be avoided.

²¹⁰⁶ Ubiquitous on Ancient Egyptian murals.

²¹⁰⁷ Effectiveness ranges from 43% (radical prostatectomy) via 59% (diabetes) to 84% (psychogenic ED). (Osterloh & Riley, 2002) Psychogenic cases who respond may develop renewed hope and get time to utilise psychological methods. King (2008, p. 697) suggests efficacy of 50% in diabetes and much lower after radical prostatectomy (esp. if nerves are not spared)

²¹⁰⁸ Some cases have genetic disorders of retinal phosphodiesterase.

²¹⁰⁹ E.g. Peyronie's disease: penile curvature due to plaque or scar; painful erection/difficult penetration; may improve spontaneously; advise continued sexual activity; delay surgery until condition stable. (Basson & Schultz, 2007)

²¹¹⁰ E.g. leukaemia, multiple myeloma, sickle cell anaemia. A post-mortem erection in men who are hung is technically a priapism and may be due to pressure on the cerebellum. Cimetidine increases sildenafil concentrations, erythromycin even more so; ketoconazole also inhibits enzyme; if necessary use low dose of sildenafil, e.g. 25 mgs.

²¹¹¹ Two case reports of prolonged erection (persisting beyond ejaculation) due to accumulation of cyclic guanosine monophosphate in peripheral nerve endings. (Goldmeier & Lamba, 2002)

Tadalafil (Cialis, 10 mg and 20 mg tablets) improves erection for *at least* 24 hours²¹¹² after taking a dose. The dose for adult (incl. elderly) men is 10 mg 30 minutes to 12 hours before intercourse. The maximum dosage frequency is once daily. It is contraindicated with organic nitrates or in the presence of significant cardio- or cerebro-vascular disease. Caution is required if used with potent CYP3A4 inhibitors, such as erythromycin. Grapefruit juice may increase plasma levels of tadalafil. Alpha-blockers should be avoided. Possible side effects include headache, dizziness, dyspepsia, flushing, nasal congestion, back/muscle pain, eyelid swelling, eye pain, and hyperaemic conjunctivae.

Vardenafil (Levitra, 5 mg, 10 mg and 20 mg tablets; PDE5 inhibitor) can be taken once daily. 10 mg (5 mg if elderly or impaired hepatic or liver function) is taken 25-60 minutes before sexual activity²¹¹³. The dose range is 5-20 mg, average 10 mg. Avoid vardenafil with nitrates/nitric oxide donors, contraindications to sexual activity (e.g. severe cardiovascular disease), severe hepatic impairment, end-stage renal disease needing dialysis, hypotension, recent CVA/MI, unstable angina, and known hereditary retinal degenerative states. Do not use vardenafil with grapefruit juice and, in the over 75s, do not use it with potent CYP3A4 inhibitors²¹¹⁴. Avoid vardenafil in patients with anatomical abnormalities or a proneness to priapism²¹¹⁵. Downward dose adjustment (5 mg) may be needed if vardenafil is co-prescribed with erythromycin. Risk-benefit analysis must be undertaken for cases with bleeding diatheses or active peptic ulcer disease. It is not recommended that vardenafil be given with alpha-blocking drugs. Adverse effects include dyspepsia, nausea, dizziness, syncope, headache, rhinitis, flushing, hypertension/hypotension, hypotonia, visual disturbance²¹¹⁶, photosensitivity reactions, and erectile disturbance. Apomorphine HCl (Uprima)²¹¹⁷, a central DA receptor agonist, was available for the treatment of ED up to 2006.

Local devices include vacuum condoms (vacuum constriction device²¹¹⁸) and penile rings may be used, although sensation may be compromised by these methods.

Alprostadil (prostaglandin E²¹¹⁹; MUSE²¹²⁰) can be used in intraurethral pellet ('stick') form²¹²¹, with erection after about 5-10 minutes; penile pain may occur. When prostaglandins (embryotoxic in animals) are used by the male and the female partner is pregnant it is advised that the foetus is protected by barrier contraception (e.g. condoms). Intracavernosal prostaglandin E1 (Alprostadil, Viridal - metabolised locally) gives a good erection (both it and papaverine produce erections lasting 30-60 mins). It may cause local pain or priapism, especially if there is no underlying vascular cause for ED.

Other local injections are also available. Self-injection of papaverine, phenoxybenzamine or phentolamine into the cavernosa at the penile base gives a normal erection, which lasts about forty minutes. Papaverine injections have been used to differentiate between neurological and vascular causes. It will not produce an erection where there is significant arterial obstruction. In males with an intact genital circulation, injections into the corpora cavernosa of either beta-blockers (phenoxybenzamine or phentolamine) or other smooth muscle relaxants (e.g. papaverine) usually produce erections sufficient for sexual intercourse. The patient or his partner is taught to give the injection. Potentially serious side effects include priapism (admit immediately, aspirate the corpus cavernosum and inject phenylephrine 5 mgs. intracavernosally – adrenaline and metaraminol are alternatives; if no success, call urologist) and penile fibrosis.

²¹¹² This 'weekend drug' has a 17.5-hour half-life.

²¹¹³ A high fat meal delays onset of action of both sildenafil and vardenafil and they should be taken on an empty stomach. This precaution is not necessary with tadalafil.

²¹¹⁴ Ritonavir, indinavir, ketoconazole, oral itraconazole.

²¹¹⁵ Leukaemia, multiple myeloma, sickle cell anaemia.

²¹¹⁶ A higher affinity for PDE5 vs. PDE6 may account for reduced visual side effects relative to sildenafil.

²¹¹⁷ One tablet was taken *sublingually* 20 minutes before the sexual act, being virtually ineffective if swallowed. According to Anonymous (2004) apomorphine improved ED to a lesser extent than sildenafil but was the only licensed oral drug for ED 'not absolutely contraindicated with nitrates'.

²¹¹⁸ Avoid these in cases of anticoagulant therapy, leukaemia, and sickle cell disease.

²¹¹⁹ Patients who do not respond to sildenafil (esp. Post-radical prostatectomy) may respond to alprostadil injected into corpora cavernosa (*Caverject*, *Viridal Duo*). King (2008, p. 696) suggests that transurethral prostaglandin E is less effective, particularly if there is poor blood supply.

²¹²⁰ Medicated Urethral System for Erection.

²¹²¹ Use applicator. Stick strength range from 125 to 1000 mcgs and the correct dose should be worked out under medical supervision.

Surgery may involve penile prostheses²¹²² (various types - inserted bilaterally in the corpora cavernosa) or vascular surgery (e.g. aorto-iliac surgery for thrombosis of a major vessel or surgery for leakage from the corpora cavernosa).

The only sexual dysfunction that can be (almost) cured completely is vaginismus: we are dealing with methods to alleviate the problem or to achieve better control. Departments of psychiatry, focused on serious mental illness as they are, rarely work with sexual problems, and special clinics are uncommon. According to some experts, up to 70% of venous leakage cases, where blood drains away from the penis too quickly, can expect improvement with surgery. However, other experts consider the results of this type of operation, and of revascularization of the corpora, to be poor.

Dyspareunia (painful intercourse) can be physical or psychological.

Priapism is the persistent, prolonged, uncontrolled and usually painful penile erection. It is a medical emergency. Half of cases are idiopathic. When due to drugs, phenothiazines are causative in 50% of cases. Diseases that can cause priapism include sickle cell anaemia, leukaemia, trauma, stroke (CVA), spinal cord injury, perineal trauma, nephrotic syndrome, multiple myeloma, and hyperviscosity states.

Some drug causes of priapism

Phosphodiesterase type-5 (PDE5) inhibitors - sildenafil, tadalafil, vardenafil.

Use and abuse of intracavernosal injections

Antipsychotics (? due to alpha 1-adrenergic antagonism) – chlorpromazine, thioridazine, mesoridazine, fluphenazine, pericyazine, promazine, thiothixene, perphenazine, clozapine, olanzapine

Butyrophenones – haloperidol

Benzisoxazole derivatives – risperidone

Antidepressants – trazodone²¹²³, phenelzine

Anxiolytics – buspirone, hydroxyzine

Anticoagulants – heparin, warfarin

Antihypertensives – prazosin, labetalol, guanethidine, hydralazine, phenoxybenzamine

Others – alcohol, cannabis, testosterone, phenytoin, black widow spider venom

Females

Dyspareunia is more common in females. It may lead to sexual dysfunction in the male partner. Vulval vestibulitis²¹²⁴ is one physical cause. Removal of a physical cause does not invariably remove the dysfunction because of conditioned anxiety (which may require couple therapy). Treatments consist of vaginal lubricants (e.g. Johnson's Baby Oil), vibrators, other sex aids, enhanced foreplay, psychotherapy aimed at improving the interpersonal relationship, family planning education, etc.

Anodyspareunia is pain from receptive anal sex and is common in gay men and may be persistent. It may lead to avoidance of anal sex or to the sole practice of insertive anal sex.

Vaginismus: The introitus tightens to prevent penetration. This is confirmed by digital examination. It can be associated with impotence or passivity in the partner (which may become obvious after treating the woman). It is often a learned phenomenon. Causes include arthritic conditions, vaginal surgery/tumour/trauma/atrophy, uterine prolapse, endometriosis, congenital problems, hymenal problems, pelvic congestion, and sexually transmitted infection. Vaginismus can cause dyspareunia and *vice versa*. Pelvic examination is performed in the presence of the partner. Hagar dilators are placed in the vagina, slowly increasing their size. However, King (2008, p. 705) states that there is 'no evidence of benefit' with dilator therapy – this does not necessarily mean that it doesn't help!

Orgasmic dysfunction is an inability to attain orgasm (*anorgasmia*) or an undue delay in attaining orgasm. Human orgasm is associated with electrical activity in the septum of the brain. As in male impotence, orgasmic dysfunction may be primary (never attained) or secondary (ability lost). The frequency and situation-behaviour (e.g. masturbation/coitus) specificity of orgasm in women is infinitely variable. About 20% never or hardly ever achieve unassisted orgasm during sexual intercourse; 30% almost always achieve

²¹²² Implants/prostheses are used less often nowadays than they were in the past.

²¹²³ Trazodone may cause pain upon ejaculation.

²¹²⁴ Multiple tiny red sores.

it, and 50% do so sometimes. The causes²¹²⁵, physical and psychological, are multiple. Studies of pudendal nerve conduction and evoked potentials can be performed if indicated. Treatment is aimed at education, reduction of fear, and enhancement of sexual arousal. Very many drugs can cause anorgasmia, e.g. SSRIs and venlafaxine. Antidepressant-induced anorgasmia may respond to cyproheptadine 2-16 mgs before sexual activity. Cyproheptadine is a serotonin antagonist and may sometimes cause a relapse of depression in individuals prone to develop it. There is no evidence to suggest that women possess a 'G spot' (Grafenberg spot) in the anterior vagina²¹²⁶.

Masters and Johnson²¹²⁷ technique: The full programme is expensive and elaborate. The basic idea is to get the couple relaxed. They avoid intercourse until everything else is satisfactory. They progress through mutual fondling (active and passive), eventually caressing breasts and genitalia (so-called *sensate focus*). This is all accompanied by therapeutic evaluation and attempts to improve general relationship problems. The initial ban on intercourse, the aim being to reduce performance anxiety, was first suggested by John Hunter in the 18th century.

Prognosis: Premature ejaculation and vaginismus do best with treatment. Impotence is less certain. Loss of libido is often refractory to help. Outcome studies are made difficult by problems of definition, reporting, and sampling as well as relationship variables (including the therapist's personality) and measurement problems.

Some unusual conditions

Pseudocyesis (phantom pregnancy), which is also found in other mammals, is basically a form of conversion hysteria with lordosis of the lumbar spine, depression of the diaphragm, and possibly aerophagy (air-swallowing). Breast changes occur in 80% of patients. The most common symptom is amenorrhoea or oligomenorrhoea. Most cases are in their twenties or thirties. Hippocrates first described the condition.

John Mason first used the term in 1923. Famous cases were said to be Mary Tudor, Queen of England (1515-1558), and Breuer's patient, Anna O²¹²⁸. The frequency of the condition is not known for sure (1 in 200/250 maternity clinic admissions). One neuroendocrine theory is that there is a dopamine deficiency²¹²⁹. Psychological explanations include an extreme desire to conceive or fear or guilt surrounding pregnancy.

Simulated pregnancy: A woman declares herself to be pregnant when she knows she is not.

Pseudopregnancy: This is due to a hormone-producing tumour.

Delusional pregnancy: A woman (or man) believes she is pregnant (even with the Messiah!) when she is clearly not. It has followed loss of a baby and rejection by the spouse in a schizophrenic Indian woman. (Shankar, 1991)

Couvade syndrome: The man has a swollen abdomen or complains of any other symptom of pregnancy or of the puerperium. The Couvade syndrome, strictly speaking refers to the swollen abdomen. It is not delusional, although delusions of male pregnancy may occur, as in schizophrenia. Similar delusions can occur in organic brain disease. The non-delusional form may be related to anxiety about the partner's pregnancy.

Spontaneous miscarriage/abortion

25% of women have a miscarriage at some stage of their lives. Relief, grief, or other psychiatric problems can follow spontaneous miscarriage. Social isolation may be an important factor in determining outcome. The role of counselling/debriefing is less certain as Lee et al (1996) found that debriefing a couple of weeks after the event had the same effect as no intervention at 4 months in a preliminary study.

32 out of 67 women interviewed 4 weeks after a spontaneous abortion were psychiatric cases (depression) as determined by the PSE. (Friedman and Gath, 1989) This was four times higher than in the general female population. All 'cases' were diagnosed as depressive. Unsurprisingly, many women had symptoms of grief.

²¹²⁵ This includes trauma (e.g. spinal cord), surgery (e.g. pelvic), peripheral neuropathy, BZDs, SSRIs, MAOIs, TCAs, D2-blocking drugs, alpha-blockers, etc.

²¹²⁶ Ernst Gräfenberg (1881-1957), German-born gynaecologist, suggested the existence of a highly excitogenic spot in 1950. One theory is that it is 1" to 3" inches above the anterior opening of the vagina. However, it has been 'discovered' at various other sites including the posterior vaginal and anterior anal walls.

²¹²⁷ William Masters (1915-2001), gynaecologist, and Virginia Johnson (b. 1925), psychologist, were married in 1969 but divorced about 30 years later.

²¹²⁸ Like many other famous people, she is said to have had numerous diseases! When Breuer tried to discharge Anna O she developed an hysterical parturition, which, according to Jones (1961), he handled by hypnosis of the patient and taking an anxious exit himself!

²¹²⁹ DA inhibits prolactin release - some workers have reported hyperprolactinaemia.

Oral contraception

Vessey ea (1985) looked at the incidence of serious psychiatric illness, as measured by first referral to hospital for specialist advice and treatment, among over 16,000 women taking part in the Oxford Family Planning Association contraceptive study. Their findings were 'reassuring with respect to oral contraceptive use'. Vessey ea (2003) found no effect of the contraceptive pill on overall mortality: however, if the patient also smoked the mortality rate was increased and more so if she smoked cigarettes heavily. The 'pill', because of the progestagen, inhibits drug metabolism. If it is stopped, the woman may need to increase the dose of a psychotropic drug. Because of increased progesterone levels during pregnancy, she may need less psychotropic drugs, but she may have an increased requirement following delivery.

Sterilisation

Females: Cooper ea (1982), in a prospective study, found that the operation does not significantly increase the likelihood of psychiatric disorder. Definite regrets were voiced in less than one in twenty cases. Certain categories of women require extra counselling prior to elective sterilisation: 0-1 children, youth, poor marital relationship, and personality disorder. Adverse factors include a poor interpersonal relationship, being pressured into having the procedure, refusal by the male partner to have a vasectomy, youthfulness, ambivalence, sterilisation hard on the heels of induced abortion, and regret when done soon after the birth of a baby that fails to survive.

Males: Men may develop cysts around the severed vas leading to post-coital pain. (Gregoire, 1999b)

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18

Borderland of medicine and psychiatry²¹³⁰

Brian O'Shea

'...so long as are the seat of disease, and the physician disregards such disorder...he clearly fails to fulfil the first indication of treatment...' (Tuke, 1892, p. 1290)

'Skill in recognizing countertransference and transference of the psychiatrist's armamentarium in.....consultation-liaison psychiatry....' (Ursano & Silberman, 2003, p. 1182)

'The burden of mental disorders is likely to have been underestimated because of inadequate appreciation of the connectedness between mental illness and other health conditions.' (Prince ea, 2007)

Liaison psychiatry has taken many forms and has developed to different levels of sophistication²¹³¹ in different locations but within the same country and internationally. Lipowski and Wise (2003) set out five major models of psychiatric consultation in the general hospital setting: patient-oriented (diagnosis, assessment, psychodynamic formulation), crisis-oriented (rapid assessment, coping and problem evaluation, immediate intervention), consultee-oriented (what problem does the referring clinician have with this patient?), situation-oriented (analysis of team-patient interface), and the expanded variety (with the patient at centre stage the consultant takes cognisance of everyone who influences the patient or is influenced by the patient).

Psychiatric disorder

- Delays recovery from medical illness and *vice versa*
- Drives up cost of hospital care
- Increases number of procedures performed

²¹³⁰ DSM-I spoke of psychosomatic disorders, DSM-II referred to psychophysiological disorders, and DSM-III included psychological factors affecting medical condition, as does DSM-IV. ICD-10 avoids the terms psychogenic and psychosomatic as specific category titles for theoretical and practical reasons, e.g. psychological factors do influence other disorders as well as those traditionally categorised under such headings. In 1833, Ralph Fletcher pointed out that the brain could exert a malevolent influence on the body. In 1981, Lipowski defined psychosomatic medicine as 'a scientific discipline concerned with the study of the relationships of biological, psychological and social determinants of health and disease. It is a set of postulates and guidelines embodying a holistic approach to the practice of medicine and it encompasses consultation liaison psychiatry'. Some people attract psychiatric referral; others, equally in need, do not.

Franz Alexander (1950; lived 1891-1964), a Chicago-based psychoanalyst (b. Budapest), offered many interesting psychoanalytical 'explanations' for (7) 'psychosomatic disorders' (peptic ulcer, ulcerative colitis, bronchial asthma, thyrotoxicosis, rheumatoid arthritis, essential hypertension, and neurodermatitis), but there is little hard evidence to support these. While we can accept that psychological distress may lead to physiological changes (e.g. anxiety to tachycardia), we do not know how the latter are translated into pathological changes. Also, we do not know for sure if so-called psychosomatic conditions are truly such or whether they represent idiosyncratic reactions of organ systems.

In 1956, Hans Selye described the 'general adaptation syndrome', the hormonally mediated somatic stress response. Alexander believed that chronic overstimulation of the sympathetic nervous system was associated with stress related diseases. An intensive study of the US Navy circa 1970 found that men with the highest number of LCUs (life change units, a measurement of life events) developed more illnesses of all kinds. Some such events are independent of the individual (whole workforce is laid off) and others are probably dependent (only one is laid off out of a force of 6,000).

Rutter ea (1970), in their Isle of Wight study, found that conditions like asthma or diabetes doubled the likelihood of psychiatric disturbance in children, while neurological disorders such as epilepsy or cerebral palsy increased the risk five fold.

²¹³¹ In many cases only the psychiatrist who is on call on that day provides a consultation service, perhaps coming in from a different hospital. At the other extreme a consultation-liaison service is delivered on site by a dedicated multidisciplinary team.

- Increases number of discharge diagnoses
- There is no direct relationship between a medical assessment of severity of illness and subjective distress
 Find out what patient expects and believes is amiss
 Patients may mask mood complaints
 Somatic illness can mimic mood disorder
 Adjustment disorders with subjective low mood in in-patients are common²¹³²
 Treatment of depression in general medical or surgical inpatients shortens hospital stay
 Many times more workdays are lost through mental ill health than through industrial disputes
 Depressive and anxiety disorders significantly limit function independently of chronic somatic disorder
 Depression comorbid with one or more chronic diseases have the worst health scores of all disease states²¹³³
 Organic psychiatric disorder, especially quiet delirium, is missed more often than are mood disorders
 GPs and house officers miss half of mood and anxiety disorders
 Personal and social costs of mental and addictive disorders resemble those for major physical illnesses like cardiovascular disease and cancer, yet are relatively poorly funded when it comes to research
 Organic brain disease increases the likelihood heightens the chances of psychiatric disorder
 Children often complain of somatic symptoms like abdominal pain, headache, and limb pains
 One-quarter of children with abdominal pains severe enough to warrant paediatric investigation develop chronic psychiatric problems

In a (non-random) community (cross-sectional) study, Surtees *et al.* (2003) found that chronic anxiety caused greater physical health limitations than chronic depression or a number of somatic disorders²¹³⁴. According to Pitt (1998) up to 30% of people over 65 years of age in general hospital wards are demented, a rate that is six times the community rate, and 10-20% of the same group have delirium.

In the US in particular, there is been a tendency to fully investigate patients for organic disorder before considering or tackling psychosocial problems. A positive psychological profile may reduce the mortality and morbidity associated with disease. (Earll & Johnston, 1993) O'Shea and Falvey (1991) and Williams *et al.* (1999) found a connection between large case notes and psychosocial deprivation and psychiatric problems in psychiatric and medico-surgical populations respectively.

Selected medico-psychiatric research finding

- 1818 Johann Heinroth uses 'psychosomatic' in reference to some causes of insomnia
 1922 Felix Deutsch uses term 'psychosomatic medicine'
 1939 Billings of Colorado General Hospital coins term 'liaison psychiatry'. (Morriss & Mayou, 1996)
 1980 Use of opiate analgesia often inadequate because of exaggerated fears of inducing dependence.
 1982 TCAs (tricyclics) as effective as H2 blockers like cimetidine for treating peptic ulceration.
 1984 Neurologists miss almost ¾ of cases of psychiatric morbidity: don't ask, not told, miss cues, or not considered.
 1986 At least 50% of patients with carcinoma of GIT are alcohol dependent
 1988 Alcohol abuse in women increases risk of breast cancer (Longnecker *et al.*, 1988)
 1990 UK: Liaison work is very variable in terms of level of development and in who provides it (sector team, junior doctors, special teams). Very often, because of the workload, liaison psychiatrists can only manage to see only emergencies. The psychiatry of old age is rather better developed than other liaison work in general hospitals.
 Pre-exposure history of excess anxiety or depression and of excess unexplained somatic complaints made plastics workers more prone to become ill after exposure to chemicals.
 Psychiatric diagnosis in A&E ward admissions associated with single status, low socioeconomic status, unemployment, not having a home, and not being registered with a GP.
 1991 Many physical complaints have no discoverable organic cause; do not automatically attribute the to 'mental' mechanisms; do not overinvestigate; early recognition/management of emotional & cultural elements important.
 Psychological stress increases risk for acute respiratory illness, but significant methodological problems.
 Psychiatric basis of some general hospital admissions is missed and psychiatric referral does not follow.
 Stress increases metastatic spread of rat mammary cancer via suppression of natural killer cell cytotoxicity.
 Chronic pain increases risk of suicide to 2-3 times the general population rate (Fishbain *et al.*, 1991)

²¹³² Use of symptom checklists potentially over-diagnose formal depressive disorders when the correct diagnosis may be difficulty adjusting to somatic illness, pain, dyspnoea, other distressing symptoms, loss of familiar environment/relationships, and a depressing hospital milieu. (Winrow & Holmes, 2005) One should not ignore the possibility of abstinence phenomena, including withdrawal from nicotine, alcohol, and prescribed or illicit substances, or iatrogenic depression.

²¹³³ See Moussavi *et al.* (2007)

²¹³⁴ Except for stroke.

- Men and women with schizophrenia have life expectancies of 57 and 65 years, living a fifth less years than otherwise expected.
- 1993 Cancer of larynx: 40% of laryngectomy patients found to be depressed, but none who received radiotherapy (Irish pilot study).
- 1994 Unemployment in previously stably employed middle-aged men led to increased mortality from both cancer and cardiovascular disorder, even after adjusting for other variables such as alcohol, tobacco and weight.
- 1995 Patients with at least 10 admissions to non-psychiatric departments during 8 year period. Of persistent somatisers, 16% were learning disabled (low IQ), 48% dependent on drugs or alcohol, and 48% were personality disordered. Main ICD diagnoses: anxiety states (54%), depressions (30%), phobias (18%), and psychosis (20%).
- 1996 Overwork can kill, especially if combined with high physical & psychological demand, low control over decisions, and low social support, including meeting colleagues socially. Mechanisms require further research.
- 1997 Alcoholics have similar medical outcomes to other patients after liver transplantation, but they are still vulnerable to alcoholic relapse; little is known about predictors.
41% and 26% of 345 consecutive patients presenting to urban teaching hospital emergency department screened positive for substances of abuse and alcohol respectively.
- 1997 German general practice study of peptic ulcer: alcohol protects against and caffeine may promote *H. pylori*! Nicotine is neutral.
- 2000 Increased risk of breast cancer if mother died during patient's childhood and if patient had a history of chronic depression.
- 2001 Mortality rate in Massachusetts among cases of severe mental disorder in 2000 was 3 times expected rate (in 25-44 year olds the cardiac-related death rate was raised more than 6-fold); main cause was cardiovascular, followed by respiratory.
- 2002 Severely stressful life experiences do not increase risk of recurrence of breast cancer.
Retrospective study of cadaveric renal transplantation at Dublin's Beaumont Hospital suggests that with comprehensive pre-transplant multidisciplinary assessment psychiatric patients can do well.
- 2003 People with schizophrenia, esp. males, have a predicted increased risk of both coronary artery disease and stroke; they have a poor diet; most smoke; most are overweight/obese.
Large Danish study of breast cancer patients finds depression to be a negative prognostic factor.
Strong inverse relationship between social support and psychiatric morbidity in people with early breast cancer.
In March, American Board of Medical Specialities approves subspecialty of psychosomatic medicine.
The more depressed is the peritoneal dialysis patient the greater is the risk of peritonitis.
- 2004 Of 200 consecutive psychiatric admissions 48.5% and 22.5% scored 'hazardous/harmful use' and 'significant dependence' respectively on Alcohol Use Disorders Identification Test (AUDIT), with no significant gender differences; alcohol misuse was strongly associated with suicidality.
Oropharyngeal (22-57%), pancreatic (33-50%), and breast (1.5-46%) cancers often associated with depression.
- 2005 SSRIs might reduce cardiovascular morbidity/mortality in depressed patients after acute MI, but controlled study needed.
Folate might protect against increased risk of breast cancer associated with alcohol consumption.
World's first partial facial transplantation performed in France by Jean-Michel Dubernard.
Excess of suicides in men aged 65 years or older with prostate cancer in Florida.
- 2006 Using Alcohol Use Disorders Identification TEST (Audit), over 36% of subjects in medical and surgical wards of an Irish hospital screened positive for either an alcohol use disorder and/or for binge drinking; male sex and under 65s were risk factors.
International school-based survey (131 countries) of 13-to-15-year-olds showed relatively narrow gap in tobacco use between the sexes, a high willingness to take up the habit, and high levels of second hand smoke exposure at home and in public places.
- 2007 Preliminary evidence that increased folate intake decreases risk for Alzheimer's disease, or at least improve information processing and sensorimotor speed in the elderly.
UK GP research database: severe mental illness associated with increased risk of death from coronary heart disease/stroke (not fully explained by medication/smoking/social deprivation); no increase in non-respiratory cancer mortality.
Norwegian study finds that folate supplementation in early pregnancy reduces risk of isolated cleft lip by a third.
Stimulant drug abuse among young adults may increase the rate of hospital admissions for stroke and related morbidity.
2177 patients with MI evaluated for ICD-10 depression and randomised to intervention or care as usual:
antidepressant therapy did not affect likelihood of depression or cardiac events. However, study lacked statistical power.
Folate-fortified cereal food reduced rate of neural tube defects in Canada.
- 2008 Follow-up of entire Swedish population 1973-2004: rheumatic disease increased risk for psychiatric disorder; SLE and ankylosing spondylitis carried higher risk of psychiatric disorder than did rheumatoid arthritis (RA); SLE increased risk for dementia and delirium; only women with RA and SLE had increased risk of psychosis and severe depression.
Large randomised Belarussian trial suggests prolonged and exclusive breastfeeding improves children's cognitive development.
36% of referrals to Irish old age psychiatry services are consultation/liason referrals but only 2 of 14 services have ring-fenced resources for consultation/liason work.
12-year follow-up of civil servants: positive affect and affect balance (between positive and negative affects) do not predict future coronary heart disease if free of heart disease at start of study but negative affect is weakly predictive.
Prospective Irish study of surgical admissions at two institutions during 2005; used HAD scale; 12.5%, 18.5%, and 8.3% had significant depression, anxiety, and mixed anxiety-depression respectively and 22.9% warranted referral to liaison psychiatry services.
Medically certified absence from work among London civil servants was associated with 1.7 times increase in mortality, whereas absence for psychiatric reasons was associated with 1.9 times increase in general mortality and 2.5 times increase in cancer mortality. (Head et al, 2008)
17% of older patients admitted for heart failure had a mental illness diagnosis and this subgroup received poorer care and was at greater risk of death and readmission than were those without a psychiatric diagnosis (Medicare patients).
Young people with new onset of panic attacks/disorder at increased risk of coronary heart disease/MI; this may reflect initial misdiagnosis of CHD as panic attacks/disorder or underlying increased risk of CHD with panic in younger people.
- 2009 Patients with advanced cancer who had dependent children were more anxious, less likely to engage in advance care planning,

- and had poorer quality of life in week before death (prospective cohort study).
- Most kidney donors have a good quality of life in the long-term.
- Only a small proportion of women planning pregnancy comply with recommendations re nutrition and lifestyle, e.g. 2.9% of those who became pregnant within 3 months of interview were taking 400 mcg or more of folic acid and consuming 4 or less units of alcohol/week
- The EUROASPIRE surveys in eight European countries found that adverse lifestyle trends persist in patients one year after a cardiac event, and that a fifth of patients still smoked and the proportion of young women smoking actually increased.
- Diet rich in fruit and vegetables, moderate drinking, tobacco avoidance, and exercising reduce risk of stroke
- Smoking nullified women's otherwise large survival advantage over men
- Depression is a risk factor for morbidity and mortality in patients with coronary heart disease, particularly following acute coronary syndrome; treatment-resistant depression may have even stronger implications
- Woman in US has face transplant for repair of damage inflicted by gunshot
- Healthy young volunteers watched comedy and stressful movie strips: laughter reduced pulse wave velocity, cortisol levels, and soluble P-selectin²¹³⁵; stress increased pulse wave velocity and decreased IL-6 status; positive cardiac effects of laughter last about half an hour
- Breast and lung cancer death risk increased in schizophrenia females and males respectively during 11-year follow-up
- Danish study suggests that treatment for heart disease offered to individuals with severe mental illness is poor
- Women with schizophrenia in Manitoba are less likely to be screened for cervical cancer than are women without schizophrenia
- Long-term cancer survivors not at increased risk for major depression but are more impaired if it occurs
- In a Swedish twin study (mean age 57 years) comorbidity between major depression (MD) and coronary artery disease (CAD) have a modest relationship over the lifespan but a stronger relationship when time-dependent models are used; sustained effect of CAD on MD risk is much stronger than the other way about; effect of MD on CAD is chiefly acute (long-term effects seem to be mediated by recurrences of MD); in males the environment (often acute effects) play a significant role in comorbidity; in females chronic effects (partly genetic) are more important; and in males, genetics play a greater role in comorbidity in younger people
- Persistent depression following hospitalisation for acute coronary syndrome increases mortality over 6.7 years follow-up
- Junior doctors lack knowledge about QTc interval in relation to antipsychotic medication and fail to identify high-risk cases
- Oestrogen plus progestin therapy in the postmenopausal female does not increase incidence of lung cancer but it does increase Mortality from lung cancer, especially from non-small cell lung cancer
- High lead levels reported in some children's cosmetics
- Cross-sectional survey of over 65s in 11 sites in 7 countries with low/middle incomes: dementia was by far the main contributor to disability; other important contributors were stroke, limb impairment, arthritis, depression, sight problems, and GIT problems
- Swedish follow-up study of males aged over 30 years finds that prostate cancer associated with threefold increase in risks for cardiovascular event and suicide; drawbacks are lack of tumour stage data and possible residual confounding
- 2010 Newcastle UK 85 year olds have significant levels of disease and impairment but good functional ability and self-rated health; percentages (M/F) with hypertension 53/60; atherosclerotic disease 55/43; osteoarthritis 43/57; cataract 39/52; ever diagnosis of cancer 20/12; and dementia 7/9
- Giving up smoking during the early stages of lung cancer is associated with improved prognosis
- Increased risk of acute MI in patients diagnosed with first hospital diagnosis of schizophrenia in Taiwan during a 6-year follow-up
- In a 1-year Scottish neurology clinic follow-up of patients, those deemed unlikely to have a neurological disorder were more likely to be those who didn't attribute symptoms to psychological factors or who were in receipt of illness-related payments
- Among primary care patients in Catalonia, quality-adjusted life-year (QALY) losses from mood disorders came second to pain-related chronic medical conditions
- World's first *full* facial transplant carried out in Barcelona, Spain by Joan Pere Barret (24-hour operation on a man with severe facial injuries)
- Greater increase in testosterone may be associated with menopausal depression
- Generalised anxiety disorder increases the risk for cardiovascular events in stable coronary heart disease outpatients
- Heart failure is an independent risk factor for incident depression in elderly subjects in this Rotterdam population-based study and use of loop diuretics in such cases reduce the risk for depression

If the patient's ideas about illness are different from the doctor's ideas then the patient is unlikely to cooperate with treatment and management. In one study (Health Education Studies Unit, 1982) this lack of commitment to doctors' instructions was most pronounced among West Indian and Irish adult patients. The concept of long-term management is foreign to most folk medicine. Traditional healers would consider it an admission of failure to continue treatment once the client became symptom-free.

<p>Screening for disease</p>

<p>Can have negative effects on mental health</p>

²¹³⁵ A cell adhesion molecule on surfaces of activated endothelial and platelet cells.

Positive results may cause upset, mitigated by adequate counselling
 False-positive results, later shown to be negative, may lead to adverse effects even when the later findings are known
 Negative results could, potentially, reinforce adverse lifestyles (e.g. smoking)

Sifneos coined the term *alexithymia*²¹³⁶ in the 1970s to describe patients who go on interminably about symptoms but describe any psychological difficulty in a superficial way; they appear to be out of touch with feelings and fantasy. *Somatisation*, on the other hand, is a complex mixture of phenomena, such as conversion-type symptoms (e.g. seizures) and amplification of normal (e.g. palpitations) and abnormal sensations (e.g. pain, etc). Somatisation is common in Western primary care in the developed world and is not confined to the Developing World. There is no convincing evidence that alexithymia explains somatisation. Medically unexplained symptoms (MUS²¹³⁷) are common and should be taken seriously, a psycho-biological model should be proffered, and, where available, cognitive therapy should be offered. Organic underpinnings are often sought and rarely missed, but psychiatric problems (particularly anxiety and depression), although common, are often missed.(Hatcher & Arroll, 2008)

Malingrophobia

Described by Issy Pilowsky of Adelaide, Australia in 1985
 Irrational and maladaptive fear of being tricked into providing health care to individuals who masquerade as sick, but either have no illness at all, or have a much less severe one than they claim
 Can get out of hand, with serious consequences for both patient and doctor

Miller ea (1985)²¹³⁸ looked at eleven ways in which people might react to stress. Subjects were asked if they had reacted in that way in general in the past 6 months and if they had reacted in that way in response to any specific life stresses. Being angry with one self or with others, rumination, use of alcohol or tobacco (see Spring ea, 2003), all discriminated between those who were well and those who were psychiatrically ill at initial interview. These items were formed into a 6-point scale of maladaptive reactions. They performed a follow-up analysis of 306 women who were well at the first interview. 35 suffered an episode of psychiatric illness (23 depression, 12 anxiety) within the subsequent year. Maladaptive reactions at the first interview predicted later illness inception, even after taking life stress into account. Such reactions seemed sometimes to lead to illness even when there was only minimal later life stress. Attempts to find coping reactions that afford protection against illness inception were unsuccessful.

Patients with chronic disease should be assisted to achieve emotional adjustment by remaining as active as possible, to accept and express feelings so as to win back control, to become involved in self-management, and to search for positive outcomes of their illness.(de Ridder ea, 2008)

In a survey of patients admitted to medical geriatric wards about 10% had an acute organic psychiatric syndrome.(Hodkinson, 1973) The chief predisposing factors were pre-existing dementia, defective hearing and vision, Parkinson's disease and advanced age. The next most common factors were pneumonia, cardiac failure, urinary tract infection, carcinomatosis, and hypokalaemia. Children develop acute organic syndromes more readily than do adults when physically ill, e.g. with fevers. Chronic disorders can cause intellectual disability, disintegrative psychosis or dementia.

Denial

Commonly reported defence mechanism in clinical medicine

²¹³⁶ This is also called somatothymia. In a small PET study of healthy female alixithymics the latter demonstrated a different pattern of cerebral activation to controls in response to emotional stimuli.(Karlsson ea, 2008)

²¹³⁷ 'MUS' represents an attempt to lump conversion, dissociative, and somatisation conditions together. Some might see this as hysteria resuscitated!

²¹³⁸ 576 Edinburgh women

Found, for example, in myocardial infarction (MI) patients, in renal transplantation and, for the graft and/or donor, in heart transplant recipients
 May have protective and adaptive functions
 Denial of fatal illness may help the patient but hamper preparation for bereavement in the spouse
 Organ transplants recipients may commit 'passive suicide' by stopping immunosuppressants
 Some kidney recipients stop immunosuppressants knowing that they can fall back on haemodialysis

Anxiety and some depression are very common for a few days after MI. Less than 20% develop a severe depressive reaction. Depressed patients may report angina²¹³⁹ more often than non-depressed cases. There is increasing evidence that post-MI depression increases the risk for subsequent coronary events. Among ninety-six unselected patients referred to a specialist clinic for recurrent or persistent abdominal pain (Gomez & Dally, 1977), only 15 were found to have organic disease.²¹⁴⁰ Individual cases may shed light on why physical problems cause psychological difficulties.²¹⁴¹ Trainee psychiatrists' case notes of are notoriously deficient in the area of physical examination, especially concerning neurological and locomotor systems.(Rigby & Oswald, 1987)

Bone-pointing syndrome

A form of giving up
 Seen in primitive societies and patients who are told of a terminal diagnosis
 Derives its name from witch doctors that point a bone at people upon whom they wish to place a spell
 Patient turns to the wall, gives terse answers, and dies quickly²¹⁴²
 Going to a prestigious treatment centre may cause a temporary, psychologically mediated remission, just as when a 'stronger' witch doctor revokes the spell of a lesser one

Biofeedback involves a measuring device and immediate delivery of feedback to the patient on his responses. It can be direct (feedback given about the disorder on symptoms to be controlled, e.g. blood pressure) or indirect (this does not measure the disorder or symptom directly). The patient is taught something which produces a desirable effect on the symptom, e.g. if you warm your hands it decreases the frequency of migraine headaches. He must convince himself of the effect through practice. There is no strong evidence to suggest that biofeedback is any better than any other form of relaxation or meditation for tension-related disorders. Focus on changing a specific EEG does not negate the fact that benefit accrues from 'repeated low-stress focused attention'.(Reeve, 2003, p. 116)

Psychoneuroimmunology

About 30% of people respond to inert placebos²¹⁴³ during clinical drug trials. The charisma of the therapist is also a significant element in treatment outcome (bedside manner). Depression commonly follows illnesses such as glandular fever, brucellosis, influenza and infectious hepatitis. Animal studies offer some evidence that the immune system can be taught to respond to simple learning techniques, as when saccharin is first paired with an immunosuppressant and then given alone with the same effect. Fawzy ea (1993) demonstrated improvement in employment of coping strategies and in immune function after a short-term group interaction in people with malignant melanoma. We all experience poor resistance to infection when tired or experiencing prolonged stress.(e.g. Cohen ea, 1999) Depressives also exhibit this tendency. Hostile marital reactions are associated with slower wound healing and muted local cytokine²¹⁴⁴ production at blister wound sites than occurs after supportive social interactions.(Kiecolt-Glaser ea, 2005) Stress may lower the rate of secretion of s-IgA.²¹⁴⁵ Even with removal of the cause the person who is unable to

²¹³⁹ It should be noted that angina can be precipitated by vivid dreams.

²¹⁴⁰ Thirty-one had depression; 21 had an anxiety neurosis; 17 had symptoms of 'hysterical' origin; and, not detected until the survey, 12 had alcoholism.

²¹⁴¹ E.g. in the case of a lady with a mastectomy, 'Her husband said to her in so many words that he wouldn't go to bed with a lopsided woman'.

²¹⁴² E.g. a tumour may not be seen to account for demise at autopsy.

²¹⁴³ Rightly or wrongly, placebo prescribing is common.(Tilburt ea, 2008)

²¹⁴⁴ IL-6, TNF- α , and IL-1 β . Depression is associated with decreased IL-6 and C reactive protein.

²¹⁴⁵ Salivary immunoglobulin A.

externalise aggression may show a continued fall in s-IgA levels. There is evidence to suggest T-lymphocyte suppression after bereavement and in major depression. These changes appear independent of variables like diet, activity, drugs taken, and alcohol and tobacco consumption. There may be impaired Type I/cellular immunity in schizophrenia. (Freudenreich ea, 2010)

Opiate abuse may directly affect susceptibility to HIV-1 infection because morphine induces a chemokine receptor that the virus utilises to enter T-lymphocytes. (Miyagi ea, 2000)

ACTH increases in response to CRF following acute stress. This leads to increased adrenal cortisol release. Raised cortisol levels temporarily suppress cellular immunity. Negative feedback reduces further CRF release, thereby stopping further cortisol release. Arginine vasopressin (AVP) is also partly responsible for adenohipophyseal ACTH release.

In situations of chronic stress, desensitisation of central and peripheral glucocorticoid receptors interferes with normal feedback. AVP and interleukin 1 activate the hypothalamico-hypophyseal axis with resultant persistence of hypercortisolaemia.

One theory of depression suggests that the activity of brain neurotransmitters change as a result of inflammatory changes.²¹⁴⁶ Pro-inflammatory cytokines lead to neural damage. In chronic cases, desensitisation of glucocorticoid receptors on neurones and immune cells leads to further damage via high cortisol levels. Antidepressants may affect cytokine release and modulate intracellular signals²¹⁴⁷ to alter pro-inflammatory cytokine synthesis.²¹⁴⁸ Raised interleukin-6 may be associated with major depression in cancer patients. (Sherman & Fisch, 2004) Fitzgerald ea (2006) found evidence for reduced cutaneous glucocorticoid receptor function in depression resistant to antidepressants, that circulating TNF-alpha²¹⁴⁹ may play an important role in this abnormality, and topical steroid efficacy is diminished in such cases. Tacrolimus (e.g. Prograf) and cyclosporine (e.g. Neoral) may cause a periventricular leucoencephalopathy with sudden change in mental state.

Observing the face

The face is normally the most accessible part of the body. The acromegalic may become unrecognisable to friends and scleroderma may mimic excessive use of Botox. Brown pigmentation may be due to a holiday in the sun or to Addison's disease but the latter is associated with greying of the oral lining.²¹⁵⁰ Vitiligo, an autoimmune-based depigmentation (especially affecting face, hands, and genitalia) with loss of melanocytes, may have severe psychological consequences, particularly in coloured patients. Specialist advice about camouflage is helpful. Hypomania and depression may be betrayed by excessive and diminished display of engagement respectively. Down's syndrome is unmistakable. Tremor of the lips may suggest dependence of alcohol and tongue protrusion and smacking of lips may point to tardive dyskinesia. The face is screwed up on one side in tic douloureux (trigeminal neuralgia). A hairless face in hypopituitarism, puffy eyelids in hypothyroidism, a look of 'surprise' (prominent eyeballs and retracted eyelids) on the face in hyperthyroidism or the expressionless facies in Parkinson's disease, the moon facies of Cushing's syndrome is accompanied by hirsutism²¹⁵¹, the intended smile replaced by a sneer in myasthenia gravis, the long thin face of dystrophia myotonica or the *tire en travers* (transverse smile) of facioscapulohumeral dystrophy, and the head may move in synchrony with the pulse in cases of aortic incompetence. Incongruous affect or blunted emotions may prompt a search for other symptoms of schizophrenia. Facial palsy may spare emotional movements or, rarely, emotional movement may be lost²¹⁵² with retained voluntary activity.

Neuroendocrinology & psychoneuroendocrinology

While neuroendocrine axes are abnormal in some patients with certain psychiatric disorders, (Arce ea, 2003) these often normalise on recovery from an illness episode, suggesting state rather than trait markers. As yet, such findings have limited clinical application.

²¹⁴⁶ Il-1 → increase in prostaglandin E2 and NO.

²¹⁴⁷ E.g. cyclic AMP and BDNF.

²¹⁴⁸ Examples of pro-inflammatory cytokines include Il-1 and -6 and TNF- α . Anti-inflammatory cytokines include Il-4, -10, and -13.

²¹⁴⁹ Depressed patients with congestive cardiac failure have raised levels of TNF- α and soluble apoptosis mediators. (Parissis ea, 2004)

²¹⁵⁰ Phenothiazines and a number of other drugs (antimalarials and anovulants) and toxins (e.g. lead) can cause oral pigmentation.

²¹⁵¹ **Hirsutism** due to ovarian causes is associated with very high serum testosterone levels whilst dehydroepiandrosterone (DHEA) levels are raised in cases associated with disease of the adrenal glands. Idiopathic/familial, polycystic ovaries, and the menopause are the most frequently encountered causes of hirsutism. There are many other causes, e.g. anorexia nervosa, acromegaly, Cushing's syndrome, congenital adrenal hyperplasia, glucocorticoids, ACTH, anabolic steroids, minoxidil, and phenytoin.

²¹⁵² With lesions affecting temporal lobe or pons.

Hypothalamico-pituitary-end organ axes

Gonadotrophin releasing hormone (GnRH) stimulates release of luteinising (LH) and follicle stimulating hormones (FSH)

GnRH controls the menstrual cycle in females (in males, secretion of testosterone and spermatogenesis)

Growth hormone releasing hormone (GHRH) stimulates growth hormone (GH) release

Somatostatin inhibits release of GH and TSH (it also has effects on various GIT structures)

Thyrotropin (TRH) releasing hormone releases TSH and prolactin

Dopamine (DA) inhibits prolactin and TSH release

DA blocking drugs such as metoclopramide and antipsychotic drugs increase the TSH response to TRH

Corticotrophin releasing hormone (CRH) stimulates release of ACTH and other POMC-related peptides

ACTH regulates adrenal cortisol secretion

Acromegaly

In acromegaly there is excess growth hormone (GH) secretion by a pituitary somatotroph adenoma or, less often, hyperplastic adenohypophyseal eosinophil cells. Growth hormone acts via insulin-like growth factor-1. Most cases are insulin resistant and one-fifth is diabetic. Facial disfigurement (e.g. widely spaced teeth) is an important issue. Macroglossia and hypertrophic pharyngeal soft tissues lead to obstructive sleep apnoea. Patients may lack spontaneity and state this may alternate with periods of elation and impulsiveness. The patient may become uncaring of others and self-centred. Eventually thinking becomes slowed. Respiratory, cardiovascular and cerebrovascular problems shorten life expectancy. Surgical interventions involve removal of small tumours via the sphenoid sinus with the addition of radiotherapy and medical therapy for partially removed larger adenomas. Bromocriptine and other dopamine agonists that inhibit GH secretion via certain somatostatin receptors have been replaced by long-acting somatostatin analogues (e.g. octreotide), and novel medications like pegvisomant (Somavert), a GH receptor antagonist. (Schreiber et al, 2007)

Metabolic syndrome (Reaven's syndrome, syndrome X, insulin resistance syndrome)

Human obesity with insulin resistance²¹⁵³, dyslipidaemia, and hypertension; measurement of abdominal obesity and fasting blood sugar are good screening tests; and weight reduction, increased physical activity, and medication review are the main indicated interventions. (Eckel et al, 2005; Straker et al, 2005) Yevtushenko et al (2008) found that leptin genotype and smoking were associated with metabolic syndrome in schizophrenia. Interacting with diet, a polymorphism in the multi-PDZ domain-containing adaptor protein (PDZK1)²¹⁵⁴ is associated with the metabolic syndrome. (Junyent et al, 2009) Low levels of vitamin D may also be important. (Reis et al, 2009) Lower levels of adiponectin²¹⁵⁵ and gain in weight after taking atypical antipsychotic drugs increased the risk of metabolic syndrome in patients with schizophrenia. (Bar et al, 2009) Metabolic syndrome is associated with stress at work (Chandola et al, 2006) and with clozapine. (Lamberti et al, 2006; Ahmed et al, 2008) Metabolic syndrome is 2-4 times more common in schizophrenic cases v controls. Type II diabetes is more common in schizophrenic patients (even before atypical antipsychotics) and in unaffected relatives of schizophrenic patients than in controls. About 15% of drug-naïve first-episode schizophrenic patients have impaired fasting glucose levels and hyperinsulinaemia. First episode schizophrenic patients have three times as much intra-abdominal fat as do matched control subjects. Meyer and Stahl (2008) reviewed the literature on metabolic syndrome in schizophrenia and found strong evidence for significant cardiometabolic risk differences among antipsychotic agents. They point out that H1 and 5-HT2C antagonism are associated with weight gain, but receptor targets for dyslipidaemia and insulin resistance (both of which may occur without weight gain with some antipsychotic drugs) are as yet unidentified.

²¹⁵³ Insulin resistance may explain most, if not all, of the syndrome. (Eckel et al, 2010)

²¹⁵⁴ This protein regulates the HDL-receptor scavenger-receptor type B class I.

²¹⁵⁵ This is a hormone derived from adipocytes and it is involved in the control of lipid and carbohydrate.

Weight gain is highest with clozapine and olanzapine, somewhat less with risperidone and quetiapine, and lower again with ziprasidone and aripiprazole.²¹⁵⁶

The clinical relevance and predictive power of the metabolic syndrome *per se* has been questioned. (Kahn, 2008; Sattar et al, 2008; Eckel, 2010; Bayturan et al, 2010) Does it really hang together, i.e. is it no better than the sum of its parts? It may be better to simply treat each abnormality appropriately.

Sensory deprivation

D. O. Hebb researched the role of prolonged sensory isolation during brainwashing.

With visual, auditory, and tactile deprivation for periods up to seven days there may develop

Increased suggestibility, anxiety, tension

Poor concentration and ability to organise thoughts

Somatic illusions

Physical complaints

Intense subjective emotional distress

Vivid (usually visual) sensory imagery

Hallucinations and delusions (sometimes)

Weaning from mechanical ventilation

A minority of patients find this difficult to tolerate. Reasons include fear of dying, depression and other negative affects such as anger, and conflicts with others. Interventions include slow, gradual weaning, dealing with conflicts, and cautious use of medication.

Hypothermia

Psychiatrists should be aware of this disorder for many reasons. A reduction in heat production may follow overdose when a patient lies on a cold floor for a long time before being discovered. A depressed or demented patient may not eat properly or attend to domestic heating. Hypothyroidism is also associated with decreased heat production. Excess heat loss may be associated with alcoholic intoxication. Giving alcohol will cause vasodilatation and increased heat loss. Failure of the brain to regulate body temperature may follow overdose with phenothiazines, barbiturates or TCAs. Drug screening should be performed. In hypothermic subjects the ECG may show rounded waves rising above the isoelectric line (J waves) where QRS complex and ST segment meet and prolongation of QT interval and QRS complex. Death is usually due to ventricular tachyarrhythmia/fibrillation/asystole. Hypothermia may simulate brain death.

Lyme disease

This is a tick transmitted spirochaetal infection caused by *Borrelia burgdorferi*.²¹⁵⁷ It is the most common European tick-borne disease. Most cases are benign and self-limiting. Delusional disorder, schizophrenia-like disorder, bipolar disorder, major depression, panic disorder, anorexia nervosa, OCD, and dementia have been reported in association with Lyme disease. 26-66% of cases develop a depressive state.

Acute pancreatitis

The most common causes are bile stones and alcohol abuse, although cigarette smoking is an independent risk factor for acute recurrent pancreatitis. (Yadav et al, 2009) Other causes are idiopathic (15-25% of cases),

²¹⁵⁶ All 6 of these drugs carry an FDA diabetes warning although the latter 2 drugs probably have the least risk of the 6 in practice.

²¹⁵⁷ **Lyme disease:** Burgdorfer described this tick-borne spirochaete in Lyme, Connecticut in 1975. The vector is the tick *Ixodes ricinus*. Any bodily organ can be affected. In most parts of Europe it is the deer that is the common carrier of the tick the main Irish reservoir is the woodland population of birds. (Cullen, 2010) Rodents are important in Central Europe. Because of rising temperatures there may be an increase in the incidence of the disease. Three stages have been described. *Erythema chronicum migrans* (rash develops days/weeks after bite and is an annular erythema that slowly spreads outwards; usually found on trunk/limbs), with or without systemic symptoms (pyrexia, headache, backache) constitutes stage one. In stage 2 there may be a fluctuating meningoencephalitis, cranial and peripheral radiculoneuropathies, mononeuritis multiplex, Guillain-Barré syndrome, and myositis. Stage 3 may develop after months to years and include oligo-articular arthritis or a chronic neurological syndrome including meningoencephalomyelitis, spastic paraparesis, seizures, ataxia and dementia. Diagnosis depends on finding raised titres. Lyme disease and syphilis may give false positive tests for each other. Early cases respond to doxycycline. Treatment with IV centrally-penetrative antibiotics such as ceftriaxone is used if there is involvement of the nervous system. Feder et al (2007) are very critical of the concept of chronic Lyme disease.

toxic (scorpion bite, organophosphates), surgery, genetic (e.g. PRSS1), infection (bacteria, viral, parasites), hypercalcaemia, hyperlipidaemia, SLE, Sjögren's syndrome, pregnancy, trauma, ischaemia, and numerous drugs, e.g. steroids, opiates, valproate, carbamazepine, lamivudine, and paracetamol. (Frossard ea, 2008)

Chronic pancreatitis

The classic sufferer is a middle-aged alcoholic male. Drinking alcohol, bending forward, and opiates (risk of addiction) relieve the pain. Despite advice, most sufferers continue to drink.

Aetiology of chronic pancreatitis

West – alcohol and cigarette smoking²¹⁵⁸

India – malnutrition, cassava

Diabetes mellitus (DM)

Maternal glucose can cross the placenta whereas insulin cannot do so. Many oral anti-DM drugs cross the placenta but are generally avoided because of potential foetal damage.

On being told of the diagnosis, patients may exhibit anger, anxiety, depression, social withdrawal, or denial. In a study of 50 insulin-dependent diabetics common symptoms were marked anergia, excessive fatigue, irritability, depression, and delayed psychosexual maturation. DM often makes the patient feel uncomfortable, reduces his functional capacity, disrupts family life, and disturbs the adolescence of those affected at an early age. Family dysfunction is associated with poor control of diabetes in juvenile-onset cases and the latter correlates with reading problems and psychiatric in child and/or parent. 10-20% of chronic cases may have cognitive impairment²¹⁵⁹ due to diseased large and small vessels. However, an (average of) 18-year follow up of 1114 cases of type I diabetes revealed no substantial²¹⁶⁰ cognitive dysfunction despite relatively frequent attacks of severe hypoglycaemia. (DCCT/EDIC²¹⁶¹ Study Research Group, 2007) Mean age of entry to the study was 27 years. Ohmann ea (2010) examined executive function and other neuropsychological and psychosocial variables in adolescents with type I diabetes and did find cognitive deficits that were independent of quality of metabolic control and disease duration. The authors suggest such deficits are due to the disease, especially when the condition has a early onset.

The diabetic way of life has its own intrinsic stresses, and the disease has direct effects on the nervous system. Abnormal eating attitudes are common in young insulin-dependent female diabetics, but are less likely in their male counterparts. Hyperglycaemia and glycosuria (which cause weight loss) and the emphasis on diet may promote eating disorder; reducing insulin intake also reduces weight (and increases the chance of complications such as retinopathy and diabetic ketoacidosis). (Goebel-Fabbri ea, 2007, p. 92) Kawakami ea (1999) followed up 2,764 male employees in a Japanese company for eight years. They were screened at entry with the Zung (self-rating) depression scale. Each year they were screened for DM. 43 developed type II DM over the study period and of these 9 have moderate/severe depression at study onset. Various factors, such as activity, alcohol, and obesity were controlled for. The 9 cases with moderate/severe depression at study onset had a 2.3 times increased risk for type II DM at follow-up relative to non-depressed/low level of depression at entry to the study. Atlantis ea (2009) in Melbourne found that depressive symptoms doubled the risk of developing diabetes on follow up in the elderly independent of antidepressant drugs. In a community follow-up study, Campayo ea (2010) reported that clinically significant depression is associated with a 65% increased risk of DM. Type A behaviour pattern in childhood DM may be associated with an increased likelihood of a hypoglycaemic response to stress. A psychiatric diagnosis was recorded in 50% of patients being assessed for pancreatic transplantation, and 25% of patients had a lifetime history of major depression. (Popkin ea, 1988) Henry Maudsley noted an excess of DM among patients with schizophrenia. (Farmer, 2003) This connection was certainly discussed before the introduction of antipsychotic drugs. (Kooy, 1919; Braceland ea, 1945) All schizophrenic patients,

²¹⁵⁸ See Yadav ea (2009).

²¹⁵⁹ Sometimes multi-infarct dementia.

²¹⁶⁰ Caveats: Higher glycosylated haemoglobin values were associated with moderately reduced motor speed and psychomotor efficiency. Pre-study test results on the small number diagnosed during childhood and information on elderly cases or those with over 30 years of illness cannot be provided by this study.

²¹⁶¹ Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications.

regardless of medication status, should be screened for diabetes. (Smith, 2008) Poor control, as illustrated by glycosylated haemoglobin levels, is more common in diabetics with a psychiatric illness. Even when compliance is controlled for, stress seems to adversely affect control. However, compliance to diet and exercise is reduced by depression. (Katon ea, 2009) Psychological factors appear to play some role in 'brittle' DM, but it should be recalled that the diabetic adolescent whose DM is difficult to control and who acts out also has labile diabetogenic hormones because he is an adolescent. (Kay & Tasman, 2006, p. 813) Psychosocial stress may play a role in precipitating the disease and in non-compliance in some cases of DM. Significant fears may develop in patients concerning blood sugar dyscontrol and complications such as blindness or amputation. Over enthusiastic control by obsessive patients may lead to persistent hyperglycaemia (to avoid low blood sugar), excessive blood sugar monitoring, and episodes of hypoglycaemia²¹⁶². Emphasis on building a relationship with the adolescent diabetic may prove better in terms of disease control than a rigid insistence on acceptable blood sugars.

Diabetes in women may cause reduced arousal, diminished vaginal lubrication, and reduced capacity for orgasm. Bulimia nervosa patients who are also diabetic may deliberately omit their insulin. Logroscino ea (2004) found that elderly women with type II DM had an increased likelihood of having poor cognitive function that gets worse over time and that oral hypoglycaemic drugs may reduce this risk. Drugs like beta-blockers may reduce arousal (and erection in the male). Sexual dysfunction may be associated with depression.

Autonomic neuropathy affecting the vagus nerve in diabetics

Tachycardia and loss of sinus arrhythmia

Later on there may be cardiac denervation²¹⁶³

Impaired reflexes, e.g. Valsalva

Postural hypotension (loss of peripheral sympathetic tone)

Polyneuropathy – warm foot with bounding pulses (vasodilatation)

In a systematic review and meta-analysis, Gillies ea (2007) found that lifestyle interventions are at least as effective as drug treatment in reducing the rate of progression to type 2 diabetes in people with impaired glucose tolerance.

Apart from universal precaution with alcohol²¹⁶⁴, the diabetic must be aware of certain facts (see table).

Alcohol

High in energy and carbohydrate

May potentiate the hypoglycaemic action of oral hypoglycaemic drugs and insulin

Produces hypoglycaemia by directly inhibiting gluconeogenesis and hepatic glucose output

Predisposes to lactic acidosis²¹⁶⁵ if taking biguanides

Can induce a disulfiram-type reaction in people on sulphonylureas

Abstinence should be the rule if the patient is obese, hypertensive, has hypertriglyceridaemia, or is alcoholic.

Aripiprazole and ziprasidone are the antipsychotics of choice in people with DM.

Use of exogenous insulin results in low C-peptide levels; oral hypoglycaemic drug use may raise C-peptide levels (mimicking insulinoma) by stimulating beta islet cells; oral hypoglycaemic drugs can be detected in blood or urine.

Nocturnal hypoglycaemia

This is common in Type 1 diabetes. It is often not detected, as it usually does not waken the patient.

Complaints include unrefreshing sleep, vivid dreams/nightmares, hangover/morning headache, and

²¹⁶² Some patients become unaware of the physiological symptoms of hypoglycaemia or cannot distinguish them from anxiety. Shame or helplessness may complicate attacks. Patients may keep their blood sugars too high so that attacks are avoided. A potentially dangerous scenario is where a diabetic ends up in an Emergency Department with hypoglycaemia but is mistaken for a fighting drunk.

²¹⁶³ This is similar to the transplanted heart.

²¹⁶⁴ E.g. alcohol is a relative contraindication to warfarin therapy – risk of bleeding. (Bloomfield ea, 2006)

²¹⁶⁵ So does paraldehyde.

tiredness. A bed partner may notice diaphoresis, restlessness, and twitching/seizures. The cause may be insulin regimen. If the patient's blood glucose level is < 6 mmol/L on retiring a carbohydrate snack should be taken. A fast-acting insulin analogue can be employed for the evening meal or depot intermediate-acting insulin can be delayed until going to bed.

Reactive (postprandial) hypoglycaemia (RH)

There is sudden weakness and faintness with anxiety 1-4 hours after a meal. Blood sugar levels rise and then fall. It can occur in otherwise healthy individuals or it can be due to rapid carbohydrate absorption as in post-gastrectomy patients. Treatment consists of a low carbohydrate diet. Often such patients are anxious and irritable between meals, and the relationship of these symptoms to RH is controversial.

Factitious hypoglycaemia

This may be induced by insulin or by oral hypoglycaemic agents. The pancreas secretes C-peptide along with insulin, so that high insulin and low C-peptide levels indicate exogenous insulin, and high insulin and high C-peptide levels indicate endogenous insulin.(Scarlett ea, 1977)

Plastic/cosmetic surgery

Cosmetic procedures in the US rose from 2.9 million in 1997 to 11.9 million in 2004. About £200 million is spent each year in the UK on cosmetic procedures and one-quarter of bank loans are procured for this purpose.(Veale, 2007, p. 617) Procedures vary from Botox injections to rhytidectomy (face-lift).

Factors associated with worse outcome after plastic surgery

Unrealistic expectations

Delusions

History of dissatisfaction with prior surgery

Suicide rates are increased in women after cosmetic breast augmentation.(Sarwer ea, 2007) Psychiatric disorders to consider body dysmorphic disorder (BDD), amputee identity disorder (AID), body sculpting, and delusional states. The first three of these phenomena are usually 'explained' as fixed (overvalued) ideas. The factitious SHAFT syndrome consists of patients who manipulate plastic surgeons into performing surgery. They patients are described as being sad, hostile, anxious, frustrating, and tenacious.(Kasdan ea, 1998)

BDD cases with have multiple complaints may shift focus to other body parts. They have rarely been known to attack their surgeons. BDD patients are often unhappy with previous surgery and may state that the wrong procedure was carried out or that the end result is worse than the original 'defect'. BDD patients may practice DIY surgery, e.g. by filing down teeth or using a staple gun on the face. The milder the symptoms and the lower the expectations of the BDD patient the safer is it to allow surgery to proceed. The attempted suicide rate is increased.(Veale ea, 1996)

AID involves the wish to have a limb(s) or digit(s) amputated. The patient may injure the body part in order to force surgery, or they may amputate the limb themselves. Such cases will often live as 'disabled' persons, e.g. residing in a wheelchair. They (unlike BDD) do not see the part to be amputated as ugly but they believe (like gender identity disorder) that will cope better without it. It should not be confused with apotemnophilia (sexual attraction to disabled persons). Psychiatric treatment is ineffective.(Smith & Fisher, 2003)

Body sculpting cases change their bodies for 'artistic' reasons or desire to take the form of an animal, e.g. the famous 'Tiger man': Dennis Smith, a San Diego computer programmer spent a small fortune on tiger-like tattoos and plastic surgery and had his name changed by deed poll to 'Cat Man'; he claimed to 'feel like a tiger'.

Facial transplantation has become a reality.²¹⁶⁶ As with other transplants, rejection is possible.(Guo ea, 2008) The psychological impact of this procedure needs to be anticipated, planned for and managed. Lay people worry lest the donor's identity is transferred with the face, but modelling procedures suggest otherwise.(Butler ea, 2005)

²¹⁶⁶ There were 13 cases up to August 2010.

Cosmetic genitoplasty for women who want a flat vulva (no protrusion beyond the labia majora) has become a 'booming business'!(Liao & Creighton, 2007) This may represent a lack of knowledge of normal variation or idealisation of a particular physiognomy.

Post-operative cognitive dysfunction

Apart from cardiac surgery (see below), this area has received little research endeavour, findings conflict, and adequate controls are needed to take variables such as disability, pain, and depression into account.(Selwood & Orrell, 2004)

Cardiac problems²¹⁶⁷

Risk factors for QTc prolongation include psychiatric drugs (e.g. thioridazine), drug-drug interactions, congenital long-QT syndrome, pre-existing heart disease, bradycardia, and low potassium or magnesium levels. Mitral regurgitation has been associated with dopamine agonists like cabergoline and with anorectic drugs such as fenfluramine.

A person whose same-sexed relatives died at a certain age may greatly fear death at that age and may take excessive precautions to prevent it, e.g. taking no exercise.

Higher baseline depressive symptoms are associated with increased progression in carotid intima-media thickness²¹⁶⁸ over the next three years.(Stewart ea, 2007) Patients with coronary artery disease who become depressed excrete increased amounts of noradrenaline in the urine.(Otte ea, 2005) Also, such patients when in possession of the s allele of 5-HTTLPR may be more vulnerable to poor outcomes.(Otte ea, 2007)

Patients in receipt of a heart transplant do not experience palpitations with anxiety because the denervated heart does not increase its rate in response to anxiety. This may change with new techniques for restoring sympathetic innervation aimed at improving cardiac response to exercise.(Bengel ea, 2001) Mai ea (1986) found a high prevalence of preoperative anxiety and depression in heart transplant patients. Transient confusional states may occur in the first days after this procedure, as can anxiety, social and behaviour problems. Higher scores on the somatic scale of the GHQ predicted a higher mortality postoperatively. The same authors suggested that certain 'preliminary' and 'tentative' psychiatric requirements before surgery should be addressed. Anxiety and depression secondary to a serious medical disorder is not a contraindication to operation. Severe personality disorder, especially if associated with recent alcohol or drug abuse, may contraindicate surgery. Less severe personality problems are a relative contraindication. Druss ea (2000) reported that patients with schizophrenia are relatively less likely to receive cardiac catheterisation after MI.

Mai (1993) reviewed the subject of heart transplants and that 45% returned to wholetime work and family and sexual problems were common after surgery. Good family and social supports are important requirements. Sound, informed motivation is needed. And, it is important that no serious cognitive dysfunction exists. Chacko ea (1996) found that DSM-III-R Axis I diagnoses predicted post-transplant hospital utilisation and Axis II diagnoses predicted post-transplant behaviour.

Psychiatrists are becoming more involved in the selection of recipients for organ transplants, the prediction of non-compliance with anti-rejection therapies (carrying ethical implications if surgery is denied), and the assessment of post-transplant rehabilitation.

*Psychiatric screening before transplant surgery*²¹⁶⁹

Picture of patient as a person

Capacity and informed consent

Coping skills

Collaborative and adherence abilities

Social supports²¹⁷⁰

Baseline mental functioning

Comorbid psychiatric disorder²¹⁷¹

²¹⁶⁷ The interface between psychiatry and the heart is reviewed in detail elsewhere.(O'Shea, 2006a,b,c) The methodological flaws (such as use of self-reports) in studies purporting to demonstrate a connection between psychological stress and heart disease have been addressed by Macleod ea.(2002)

²¹⁶⁸ Measured by ultrasound.

²¹⁶⁹ Various instruments may be employed, e.g. Psychosocial Assessment of Candidates for Transplant or PACT.(Olbrisch ea, 1989)

²¹⁷⁰ According to Dickens ea (2004) people who do not have a confiding relationship before an MI were at greater risk of further cardiac events.

Substance abuse and ability to stay of substances long-term
 Ability to modify behaviours such as exercise and smoking
 Patient and family requirements during various stages
 Plan services to meet needs

Patients sometimes worry that someone had to die so that they could receive an (cadaveric) organ or that they will somehow take on the characteristics of the donor.

Bass (1986) considered that most patients derive psychological and social benefit from coronary artery bypass grafting (CABG). Those who fare badly are likely to have evidence of pre-operative psychological maladjustment, and to suffer forced retirement (for whatever reason) following surgery. Some develop CNS complications, at least in the short term, (Walzer ea, 1997) especially with a long duration of extracorporeal circulation, microemboli (calcific plaque, platelet aggregates, air from oxygenator), hypotension, a low haematocrit, and metabolic disturbances. Depression following CABG is an important independent predictor of death. (Blumenthal ea, 2003) Post-CABG depression may respond to CBT. (Freedland ea, 2009)

Possible causes of neurological damage from heart surgery (Swain, 1993)
 Damage to diseased vessels or intracardiac entrapment of air or particles
 Microemboli produced by interactions between blood and artificial surfaces in cardiopulmonary bypass circuit
 Changes in blood flow and distribution
 Other factors, such as sleep deprivation, neuroleptics, anxiety, pain, and isolation from family

Open-heart surgery, such as valve replacement, may cause more neurological insults than closed surgery, such as CABG.

Factors associated with:

Failure to return to work after operation

Socio-demographic - low socioeconomic status²¹⁷²; age > 55 years; unemployment for 6 months or more before operation; receiving disability pension preoperatively

Clinical - more medical problems and more frequent hospitalisation in previous 5 years; less improvement in cardiac symptoms after surgery; injudicious medical advice

Attitudinal - patient blames coronary disease on work stress; refuses to enter rehabilitation programme after operation; employer has a negative attitude

Return to work

Working before surgery

Short wait for operation

No dyspnoea

Low physical morbidity

Shaw ea (1986) found neurological disorders not to be a major cause of failure to return to work by six months after coronary artery bypass surgery. The long-term prognosis for early postoperative neurological disorders was found to be favourable, except in those patients who had sustained major perioperative stroke.

Bodily change of any variety requires adjustment, and the actual changes appear to be less important than our perception of such changes. (Abram, 1970; Cohen ea, 2009) The wearing of external devices may cause increased vigilance, overdependence on caring staff, fear of being far from the hospital, anxiety and panic, as well as acting to distance the partner from sexual involvement with the patient. CABG or MI are not

²¹⁷¹ Do not use St John's Wort in depressed transplant patients as it may lead to decreased immunosuppressant drug (cyclosporine) levels with consequent graft rejection.

²¹⁷² Pagano ea (2009) looked at over 44,000 adults undergoing heart surgery in part of England during 1997-2007 and found that smoking, extremes of BMI, and diabetes were associated with poor survival after surgery but that social deprivation was an important predictor of mortality risk independent of these variables.

uncommonly associated with PTSD symptoms and intra-aortic balloon pumps or frequently discharging automatic implanted cardiac defibrillators can cause anxiety.(Huffman ea, 2004)

A lower incidence of cardiac problems was found in the early 1960s among Irishmen in Ireland versus their brethren who had gone to Boston, Mass. Other factors incriminated in the genesis of heart disease are well known, e.g. cigarette smoking. Alcohol intemperance is strongly associated with sudden death post-MI. Up to 45% of patients with coronary heart disease (CHD) may become depressed.(Dowlati ea, 2010)

Depression increases the likelihood of developing CHD (Bass, 2007, p. 367) and also increases mortality after infarction.(e.g. Frasure-Smith & Lespérance, 2003) possibly due to increased platelet activation and responsiveness as a result of serotonergic dysfunction; increased platelet binding has reversed during paroxetine treatment. Failure to take exercise is a factor in the exacerbation of pre-existing heart disease in depressed individuals.(Whooley ea, 2008) A meta-analysis of 4 placebo-controlled RCTs of reasonable duration using mirtazapine, citalopram, fluoxetine, and sertraline in patients with documented CHD and DSM-IV depression (Dowlati ea, 2010) found that antidepressants were superior to placebo for decreasing Hamilton and Beck depression scale scores and produced more responses and remissions than did placebo and with no significant differences in overall dropouts or in dropouts due to adverse events.

Type A personality²¹⁷³ has been stressed as having an important aetiological role in the genesis of heart disease, although evidence is lacking.(Bass, 2007, p. 367) Stress and change are important here. Intense anger may precipitate MI. Hostility seems to be risk factor not only for CHD but for nearly every somatic disorder! Just to confuse the reader, a *type D personality* (D for distressed) has been described that may be associated with poor survival in CHD, as well as (with cardiac history and prior depression) persistence of depressive symptoms during the year following MI.(Martens ea, 2008) Such people are worriers, gloomy, unhappy, irritable, socially avoidant, and inhibit their feelings. There is a need for studies to tease out state from trait markers in this population. In post-MI depression, somatic affective symptoms are more closely linked to MI severity and cardiovascular prognosis than are cognitive affective symptoms.(Martens ea, 2010)

Factors suggested by Cohen (2003, p. 154) as increasing cardiac mortality in depressed people

Poor medication and exercise compliance

Changes in autonomic tone (with risk of fatal arrhythmia)

Increased tendency of platelets to aggregate (reduced by antidepressants – platelets contain 5-HT²¹⁷⁴)

Unfavourable changes in lipid metabolism

Presence of subclinical cerebrovascular disease

Osborn ea (2006) found that excess risk factors for CHD in people with severe mental illness were not completely explained by medication or socio-economic deprivation; such cases need to be medically screened and to have relevant interventions for diet, exercise, diabetes and smoking.

Many different illnesses have reportedly followed in the wake of significant life events. In the early 1970s it was reported, after questioning close relatives, that patients who died after MI had higher LCU scores in the half to 1 ½ years before infarction than did those surviving a similar incident. Earlier, it was reported that widowers over the age of 55 years died at 40% above the expected rate for people of the same age during the 6 months following bereavement. The excess mortality was attributed to heart disease. If they survived this time their mortality rate fell back to that found in the general population. Depression may be an independent risk factor for ischaemic heart disease in men. Different studies found this to be so for both sexes (Ford & Mead, 1998), if more so for men, but other research did not come to this conclusion for women.(Hippisley-Cox ea, 1998)

Should a person view their first MI as the start of a longterm disability he is less likely to return to work and more likely to develop sexual dysfunction. Sexual intercourse following MI can commence, gradually and gently, when the male patient can climb a flight of stairs without symptoms. Strenuous activity is best avoided. Intercourse after a heavy meal or alcohol may cause problems. Isosorbide dinitrate taken 10 minutes before sex has been recommended for those experiencing angina during intercourse. A follow up of patients with coronary artery disease who had ischaemia induced by mental stress at baseline showed

²¹⁷³ In this context there are, or rather were, only two types - A and B, B not having A's characteristics.

²¹⁷⁴ SSRIs reduce risk of re-infarction and death in depressed post-MI patients.(Taylor ea, 2005)

that they had significantly higher rates of subsequent fatal and non-fatal cardiac events that could not be explained by a number of other variables.(Jiang ea, 1996)

Anxiety is very common in cases of coronary artery disease and it negatively influences outcome. High levels of anxiety following an MI significantly increases morbidity and mortality.(Moser & Dracup, 1996) Marital stress in middle-aged women who had been hospitalised for MI or unstable angina tripled the risk for recurrent coronary events compared to women with no marital stress.(Orth-Gomér ea, 2000) Serious ventricular arrhythmia may be more likely after major stressors, e.g. the World Trade Centre attack²¹⁷⁵.(Steinberg ea, 2005)

Psychological interventions to help prevent cardiac morbidity and mortality should be individually tailored²¹⁷⁶. Cognitive-behavioural and pharmacological (e.g. antidepressants) approaches may be employed.(Mayou, 1996) All TCAs prolong cardiac conduction. There is also some evidence that the SSRI citalopram may prolong the QTc interval in dogs with resultant ventricular arrhythmias.(Brown ea, 2000) Stopping TCAs suddenly can lead to cardiac arrhythmias and influenza-like symptoms. Relatively safe antidepressant drugs in the face of cardiac conduction problems include trazodone, fluoxetine, and bupropion.

The Irish Medicines Board (2007) issued conclusions regarding use of haloperidol, pimozone, sertindole or ziprasidone (avoid with significant cardiovascular disease, QTc interval prolongation, history of ventricular arrhythmias or *torsades de pointes*, uncorrected hypokalaemia, or patient on other drugs known to prolong QT interval).

Myocarditis has many causes (infective, radiation, autoimmune, idiopathic) including drugs such as clozapine, modafinil, sulphonamides, penicillin, methyl dopa, and anti-TB drugs. Among secondary causes of cardiomyopathy are alcohol, cocaine, and cobalt.

*Tako-tsubo*²¹⁷⁷ (or *stress*) *cardiomyopathy* (Kurusu ea, 2002) is an acute, reversible condition occurring mainly in middle-aged or elderly women that may follow severe psychic stress. There is ballooning of the apex of the left ventricle. The coronary arteries are normal.

Stokes-Adams attacks

Complete heart block, Mobitz type II second-degree atrioventricular block, or sick sinus syndrome (sinoatrial disease) *with* episodic ventricular asystole

Sudden unconsciousness +/- falling

Seizures (ischaemia) in prolonged cases

Pale and death-like

Flushing during recovery (recovery much faster than in epilepsy)

Differential diagnosis: vasovagal attacks, carotid sinus syndrome

Atrial fibrillation (A Fib)

Alcohol is associated with A Fib

Multiple factors often contribute e.g. an alcoholic hypertensive with CHD

Chest pain

At least half of cardiology outpatient referrals for chest pain have a non-cardiac aetiology.(Bass & Mayou, 2002)

Common causes of chest pain

Oesophageal reflux or dysmotility

Musculoskeletal, e.g. chondritis and muscle tension

Thoracic spine disorders

Hyperventilation

Psychiatric, e.g. panic attacks²¹⁷⁸ and depression

²¹⁷⁵ The patients had implantable defibrillators.

²¹⁷⁶ When angina patients' friends have negative views of damage caused by this symptom and believe that work should be avoided it is necessary to challenge such views.(Petrie ea, 2002)

²¹⁷⁷ Japanese: *octopus trap*.

It is important not to create an invalid out of the patient by giving a false diagnosis of angina. Exercise should not be prohibited. A firm non-cardiac diagnosis should be made when appropriate and advice between treating agencies should be co-ordinated.

Deafferentiation pain

Central (due to damaged somatosensory pathways) pain

Follows injury to peripheral or central nervous systems

Associated sensations include dysesthesia (unpleasant sensations), causalgia²¹⁷⁹ (continuous, burning pain – allodynia, glossy skin and sympathetic dysfunction may be associated features), allodynia, and/or formication

Hypertension

It is possible that prolonged stress may produce a reactive hypertensive state that causes secondary changes in the vessels and kidneys leading to permanent hypertension. Transient stress is postulated by some to cause changes in renal function that may interfere with blood pressure (BP) regulation. However, the diagnosis of hypertension and its treatment may account for much of the excess of psychiatric symptoms described in this population. EPI (Eysenck Personality Inventory) scores are generally high for extraversion in hypertensive populations. Findings of ‘positive affect’ in hypertensive community-based elders were based on a single evaluation of small numbers.(Jorm, 2001) Various psychosocial upheavals, such as migration, are also associated with an increased risk of developing high BP.

Some environmental correlates of hypertension

Excess alcohol intake

Obesity (use a wide cuff) +/- sleep apnoea

Hugh dietary sodium (migration to cities is associated with increased intake)

Acute rise in BP associated with pain or psychosocial stress

One primary care study found an increased prevalence of panic attacks in hypertensives compared to normotensives, panic usually postdating a diagnosis of hypertension.(Davies ea, 1999) A prospective study found that symptoms of anxiety and depression predicted lower systolic BP eleven years later.(Hildrum ea, 2008) A family history of hypertension, or a tendency to hypertension (borderline hypertension), may be associated with retention of sodium and water whilst competitive tasks are being undertaken. Mild to moderate hypertension, with a diastolic BP of less than 110 mmHg was said to be associated with only uncertain benefit from drugs.

Raised BP appears to be associated with white matter brain lesions on MRI.(Kuller ea, 2010)

Advice to the patient

Reduce weight

Reduce alcohol intake (alcohol acutely raises BP; intake of alcohol is higher in people with raised BP; and BP falls by 5-10 mm Hg on reducing or stopping regular alcohol intake²¹⁸⁰)

Stop smoking

Restrict dietary salt

Undertake relaxation-training, e.g. breathing exercises, deep muscle relaxation, biofeedback, stress management, and cognitive strategies

²¹⁷⁸ Nocturnal (in slow wave sleep) panic attacks may fuel fears of sleep if they are misinterpreted as being cardiogenic.

²¹⁷⁹ Also called complex regional pain syndrome (CRPS) type II. CRPS I is another name for reflex sympathetic dystrophy.

²¹⁸⁰ Cervilla ea (2000) suggest that reducing systolic blood pressure and taking moderate amounts of alcohol may improve late-life cognitive outcome. Extrapolations from studies showing a correlation between moderate drinking and better health may be hazardous, e.g. there may be something about moderate drinkers that offer a better explanation for good health, such as personality, genes or exercise.

Whilst the clinician is encouraged to follow up hypertensives and encourage the continued practice of relaxation, the evidence that relaxation therapies significantly reduce BP is controversial. (Littman & Ketterer, 1999)

Drugs such as TCAs that block catecholamine reuptake reduce the antihypertensive effects of clonidine and guanethidine. TCAs increase circulating catecholamines and can therefore exacerbate the features of a phaeochromocytoma. ECT should be avoided in a patient with phaeochromocytoma.

Hypertensive encephalopathy

Rare

Associated with accelerated phase (malignant) hypertension

High BP

Neurological symptoms (usually reversible on achieving BP control) – confusion/coma, transient speech/visual dysfunction, paraesthesiae, seizures

Commonly have papilloedema

CT – may have bleeding around basal ganglia

Hypotension

A strong relationship between low systolic blood pressure and minor psychological dysfunction on the 30-item GHQ has been reported among London civil servants. Also, associated physical symptoms, like dizziness, were attributed to mental disturbance. (Pilgrim *et al*, 1992) In fact, low blood pressure may present as fatigue, 'low positive affect', (Jorm, 2001) reduced motivation, or falls. It may be orthostatic or non-postural. When due to MAOIs it may be mistaken for an exacerbation of depression. Barrett-Connor and Palinkas (1994) found an association between low diastolic blood pressure in older community-dwelling males and non-drug-related depression but the direction of causation was unclear. Hildrum *et al* (2007) found an association between low blood pressure and anxiety and depression in elderly people regardless of whether they had cardiovascular disease. Postural hypotension and electrolyte imbalance in the infirm elderly during hot weather may respond to a reduction in diuretic dosage.

Paradoxical hypotension may occur when adrenaline is given with a low potency antipsychotic drug: the beta-adrenergic stimulating vasodilator action of adrenaline is unopposed by its expected pressor action because the antipsychotic drug is occupying alpha-1 adrenergic receptors. The same result occurs when a low potency antipsychotic drug is given to a patient with phaeochromocytoma. Low potency antipsychotic drugs may cause hypotension when combined with various anaesthetics, e.g. halothane.

Urinary system

Numerous psychological issues can affect the patient with renal disease: losses (e.g. of health or transplant), guilt (e.g. re donor), uncertainty (e.g. waiting lists), mortality (e.g. death of other patients), medical care (e.g. availability of transplants, fluid restriction), phobia (of needles), and other people (e.g. getting time off work for dialysis or kidney donation from a live relative). (Butler, 2007, p. 509) Renal transplants eventually fail despite compliance with immunosuppressive therapy (a quarter at 5 years and over half at 10 years). This may not be a major issue with geriatric recipients.

Should a patient in renal failure require sedation a drug that is chiefly metabolised by the liver should be used, such as nitrazepam or chloral betaine (cloral betaine). Drugs such as ephedrine and indinavir are rare causes of renal stone formation. Acute renal failure has been reported after an alcoholic binge. In cases of benign prostatic hypertrophy, sudden urinary retention with a distended and painful bladder can follow excess alcohol intake (or constipation or prostatic infection).

Focal segmental glomerulosclerosis – some associations

Severe obesity

Heroin abuse

HIV

At least one-half of males with advanced chronic renal disease or on haemodialysis experience erectile dysfunction/decreased sex drive. (Goddard *et al*, 2006)

There is no evidence for a psychogenic mechanism in the *urethral syndrome*²¹⁸¹ (usually a female with symptoms suggesting cystitis/urethritis and a sterile urine).

Causes of syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Idiopathic

Drugs – TCAs, SSRIs²¹⁸², carbamazepine, haloperidol, hypoglycaemic drugs (e.g. chlorpropamide), opiates, vincristine, cyclophosphamide

Psychotic disorders

CNS disorders – infection, trauma, CVA

Lung disorders – TB, pneumonia

Neoplasia – small-cell carcinoma of lung

Post-surgery

Acute porphyria

Other causes of continuous nausea/pain/stress

Renal dialysis is of no therapeutic benefit in schizophrenia. (Carpenter ea, 1983)

Aristolochic acid is found in fungus-contaminated Chinese herbs used for slimming purposes and severe nephropathy and associated tumours of uroepithelium. Balkan nephropathy, found in the flooded plains of the Balkans, probably has the same aetiology although the acid probably comes from shallow wells in this instance.

Uroepithelial tumours are associated with cigarette smoking, phenacetin, cyclophosphamide, bilharzia, industrial (e.g. rubber) poisons, and aristolochic acid.

Prostatodynia²¹⁸³, a somatoform disorder, occurs in males and is characterised by urogenital pain and urinary symptoms. It may respond to fluvoxamine. (Turkington ea, 2002) However, persistent prostate pain may follow bacterial prostatitis despite resolution of active infection and such cases have been known to respond to amitriptyline and carbamazepine.

Myoglobin levels are raised in NMS and in patients in restraints or in those taking LSD, PCP, or cocaine. Myoglobinuric acute tubular necrosis (ATN) may follow muscle injury from heroin abuse. Lithium may also cause ATN.

The urine of chronic stimulant abusers may have a stale smell due to the ammonia used in illegal manufacturing processes.

Haematology

Non-specific symptoms of anaemia²¹⁸⁴ may mimic psychiatric or neurological disorder. Macrocytic anaemia, which may be associated with dementia, may be due to vitamin deficiency, hypothyroidism, or alcohol. Haemolytic anaemia²¹⁸⁵ may be due to drugs such as methyl dopa, L-DOPA, chlorpromazine, and phenytoin. Leucopaenia/agranulocytosis or thrombocytopaenia may follow use of such agents as phenothiazines, clozapine, and carbamazepine whereas leucocytosis is found with lithium or solvents and in the DTs and the neuroleptic malignant syndrome (NMS). The prothrombin time is elevated in cases of severe liver damage. Serum amylase levels may be increased in bulimia nervosa (BN). Bicarbonate levels may also be increased in BN, psychogenic emesis, or patients abusing laxatives. Bicarbonate levels are decreased due to hyperventilation, panic disorder, and abuse of anabolic steroids. Low calcium levels occur during chronic laxative abuse. CPK is raised in rhabdomyolysis (e.g. in substance abuse), NMS, dystonia, restraint, intramuscular injection, and asymptotically with antipsychotic medications. The level of alkaline phosphatase is raised in various bone, liver, and cardiac disorders and in patients taking phenothiazines and it is decreased in pernicious anaemia.

²¹⁸¹ Causes likely include intermittent or scanty bacteriuria, difficult to grow organisms like *Chlamydia* or some anaerobes, reactions to chemicals, sexual intercourse, and atrophic vaginitis.

²¹⁸² Especially in the elderly: SSRIs can cause or exacerbate SIADH.

²¹⁸³ This is also spelled prostatodynia.

²¹⁸⁴ Malaise, apathy, confusion, self-neglect, reduced mobility, falling, etc. Of course, significant anaemia may follow bruising due to falling, particularly if warfarin or anti-platelet drugs are being taken.

²¹⁸⁵ Test: direct and indirect Coomb's test.

Porphobilinogen deaminase²¹⁸⁶ is decreased in patients with acute intermittent porphyria. Porphyria may be mimicked by plumbism and by hereditary tyrosinaemia.

The effects of haemophilia A are usually only noticed when children start to move about and can easily be mistaken for child abuse. Haemophiliac children, some of whom may have HIV infection, may have less behavioural problems than diabetic children.(Logan ea, 1990) Recombinant erythropoietin may be associated with visual hallucinations and leucoencephalopathy.(Bent ea, 1999)

The Irish Blood Transfusion Service (IBTS) currently does not accept blood donations from gay people.

Liver failure

Asterixis involves a sudden loss of muscle tone followed by its quick recovery. It can occur with encephalopathic states, neurodegenerative diseases, and with drug (e.g. opiate, anticonvulsants) poisoning. Steatosis (fat deposition in hepatic cells) is nearly always present in heavy drinkers of alcohol, even those with liver function tests with normal limits. Alcoholic hepatitis, even in the absence of cirrhosis, can lead to fatal hepatic or renal failure or bleeding from varices. Elevated INR in alcoholics may be due to hepatic insufficiency or vitamin K deficiency.

Haemochromatosis is an autosomal recessive disorder characterised by excessive absorption of iron. Abuse of alcohol, which is said to be common in patients with haemochromatosis, increases iron absorption further.²¹⁸⁷ Iron is deposited in the tissues and it probably precipitates fibrosis. Serum ferritin levels are high. A combination of melanin and iron confers a slate-grey discolouration on the skin. Complications include hepatic cirrhosis, diabetes mellitus (*bronze diabetes*), gynaecomastia, atrophy of the testes, hypopituitarism, loss of body hair, cardiac failure and arrhythmias, and (in 30% of cirrhotic cases) hepatocellular carcinoma. Also, chondrocalcinosis (calcium pyrophosphate) deposition causes arthropathy. Liver biopsy is the main investigatory tool.

Alcoholic liver disease is sometimes associated with a prolonged QT interval with attendant risk of sudden death.(Day ea, 1993)

Anabolic steroids can cause cholestatic jaundice and a severe acute hepatitis with hepatocellular necrosis can follow abuse of ecstasy or cocaine.

Reducing pack sizes of paracetamol following 1998 legislation in the UK reduced liver transplant rates for poisoning by that drug by two-thirds.(Hawton ea, 2001) The older TCAs were probably safer in liver disease than lofepramine or the MAOIs. Acute alcoholic intoxication may reduce hepatic TCA metabolism (increased blood levels) but chronic alcohol intake may induce liver enzymes and speed up TCA metabolism (reduced blood levels). Haloperidol is safer than the phenothiazines. Clozapine, which should be avoided in cases of severe hepatic failure, may cause reversible hepatitis, eosinophilia, and a rise in aspartate aminotransferase levels. Chlormethiazole (clomethiazole) dosage should be kept low. Lithium distribution is affected by ascites, and *higher* doses of lithium are needed to produce desired plasma levels.(Leipzig, 1990) Pemoline should be avoided in people with liver disease. It can cause an asymptomatic increase in liver enzymes or, in 2% of patients, an unpredictable and perhaps autoimmune fulminant liver failure. Nefazodone (withdrawn, 2003) caused catastrophic hepatic failure in a few people with no known risk factors. Lower protein levels associated with hepatic disease may increase (unbound) drug potency; venlafaxine is relatively safe in this regard because relatively little is protein bound. Hepatic enzyme induction (e.g. by nicotine, carbamazepine, phenytoin, and barbiturates) increases drug metabolism and necessitates dosage increases.

Drug metabolism – phases

- I. Isoenzymes of the mixed-function oxidase (cytochrome P450) system – deamination, sulphoxidation, dealkylation, hydroxylation, etc
- II. Conjugation – sulphatation, acetylation, glucuronidation, methylation, etc

Oxidation by microsomal enzymes decreases with increasing age. Glucuronide conjugation (spared in most liver disease) renders compounds water soluble and hence excretable by the kidneys. Oxazepam,

²¹⁸⁶ Erythrocyte uroporphyrinogen-1-synthetase.

²¹⁸⁷ Indeed, lesser degrees of iron deposition in other cirrhosis cases (especially alcohol-related) may lead to diagnostic confusion. Secondary iron overload (haemosiderosis) spares the pancreas.

temazepam and lorazepam (short acting benzodiazepines [BZDs], conjugated only) are safer than other, long acting, BZDs such as diazepam (oxygenated and conjugated).

Non-alcoholic fatty liver disease (NAFLD)

NAFLD affects rich societies and is usually associated with insulin resistance. It is becoming more common as we become more obese. It is classified into simple fatty liver disease (relatively good prognosis) and non-alcoholic steatohepatitis (associated with fibrosis and cirrhosis). Most cases present with no symptoms but raised LFTs. Liver cancer may complicate NAFLD cirrhosis. It should be noted that alcohol consumption and a raised BMI, both of which are related to liver disease, appear to have a super-additive effect when combined, i.e. their combined effect in producing hepatic disease is greater than the sum of their separate effects.(Hart et al, 2010)

Liver transplantation

Paracetamol overdose is a common reason for this procedure. Because patients with liver transplants do as well as other transplant patients²¹⁸⁸, Lloyd (2007, p. 423) argues that they should not be excluded from such programmes. However, allocation of transplant liver should be on the basis of likelihood of best outcome. Most centres require 6 months abstinence from alcohol before transplantation, which sometimes makes transplantation unnecessary. Previous substance misuse or current methadone maintenance, as long as the patient can be expected to stick to the immunosuppressive regimen, are not contraindications. Live donors are often emotionally invested in the recipient. It is important to ensure that the liver tissue is freely given: no threats and no payment.

Thyroid

Globally, iodine deficiency is among the most common preventable causes of intellectual disability (mental retardation: Hetzel, 1988; Haddow et al, 1999) Loss of weight is common to primary anxiety and hyperthyroidism but appetite is usually increased and reduced in hyperthyroidism and primary anxiety respectively. Rarely, cases of hyperthyroidism in middle age or the elderly may present with lassitude, slowed mentation, depression (*apathetic* or *lethargic hyperthyroidism*), weight loss, atrial fibrillation and congestive cardiac failure. Eye signs may be absent. Younger patients may present with agitated depression. The tremulous patient with unstable emotions may be mistakenly assumed to be drinking to excess. The psychiatric manifestations are likely to result from central metabolic effects of excess T4 and the actions of catecholamines since beta-blockers alleviate psychiatric symptoms without affecting thyroid hormone concentrations.(Trzepacz et al, 1988) T4 levels may be raised by anovulants or other oestrogen-containing drugs, phenothiazines, clofibrate, or by pregnancy²¹⁸⁹. The anti-epileptic drug tiagabine is a rare cause of goitre. In the presence of hypothyroidism plus depression, antidepressants tend not to be effective. Pregnancy often necessitates an increase in dosage of thyroid hormone to maintain a normal TSH level and to prevent adverse cognitive outcome in offspring.

In the case of gravid women taking lithium, a foetal goitre may compress the trachea during delivery.

‘Myxoedematous madness’, a global term for a wide variety of psychotic manifestations (affective, schizophreniform, delirious, etc) of hypothyroidism, was coined by Richard Asher.(1949)

Pendular reflexes (delayed relaxation phase) are found in hypothyroidism, diabetes mellitus, and anorexia nervosa.(Larner, 1995)

Postpartum thyroiditis, a lymphocytic thyroiditis, may cause hyperthyroidism, hypothyroidism, or one followed by the other following pregnancy. It can be misdiagnosed as postpartum depression. While it is usually transient it can give rise to permanent under-activity of the thyroid gland when antibodies are present. It is probably due to necessary immune changes associated with being pregnant.

²¹⁸⁸ Less than 5% of grafts are lost within 5 years due to alcohol.(Lloyd, 2007, p. 426) Personality disorder, not keeping appointments, and non-compliance with medication may predict a return to drinking.(Gish et al, 2001)

²¹⁸⁹ Increase in binding globulin – free thyroxine index will correct for this.

675

Congenital hypothyroidism (1 in 3500 births) is routinely screened for at birth in developed countries. Early thyroid hormone replacement will prevent cretinism²¹⁹⁰ (neurological and intellectual damage).

Parathyroid glands

Depression is found in about a third of cases of primary hyperparathyroidism, severity of depression and cognitive problems roughly correlating with serum calcium level²¹⁹¹. In most cases depression abates on correcting the calcium level²¹⁹², but an antidepressant is sometimes required.

There are a number of causes of hypoparathyroidism. Of particular interest to psychiatrists, two related syndromes involving rearrangements and microdeletions on chromosome 22, DiGeorge and velocardiofacial, affect the development of third and fourth branchial arches. This leads to various degrees of hypoplasia of thyroid and parathyroid glands.

Burns

Most burn victims adjust relatively well. (Altier ea, 2002)

Children

Burns associated with psychiatric problems in child (e.g. mental retardation or hyperactivity) or with parental factors (e.g. abuse or neglect)

Adults

Many burn victims have pre-existing psychopathology, substance abuse, or medical illness (Stoddard & Fricchione, 2004)

Healthcare workers

Latter when they were exposed to severe burn cases following air disaster were at risk for PTSD (Epstein ea, 1998)

Burned children are more likely to develop PTSD than are burned adults. In adults, burns may be associated with alcohol or drug use, dementia, epilepsy or deliberate self-harm. Self-immolation is typically a female problem in Israel. Severe psychological problems may be associated with severe burns and their protracted treatment, especially if they involve the face. PTSD may not develop until after discharge from hospital. Organic syndromes and denial may complicate the early course.

Determinants of psychological needs of patient in burns unit

Ability to cope with stress

Event factors e.g. degree of trauma

Environmental factors e.g. family support

Painful treatment procedures

Protracted hospital stay

Disfigurement

Pre-existing problems e.g. epilepsy, dementia, intellectual disability, and alcoholism

Dermatology



²¹⁹⁰ A child with cretinism. Features include hypotonia, coarse facial appearance, macroglossia, and umbilical hernia. The derivation of the word is disputed, e.g. *creta* (Latin for chalk – pallor) or *creatus* (Latin for creature) or the island of Crete or a reference to iodine-poor soil.

²¹⁹¹ Hoogendijk ea (2008) found an association between being depressed and severity of depression on the one hand and low serum 25-hydroxyvitamin D levels and increased parathyroid hormone on the other hand in Dutch older adults (community-based 65-95 years).

²¹⁹² It should be noted that lithium may cause hypercalcaemia.

Dermatitis artefacta (factitious dermatitis): A of people with self-inflicted skin lesions have long-term psychiatric disorders that tend to respond more to change in life circumstances than to formal treatment. At least some cases of psychogenic purpura²¹⁹³ are cases of dermatitis artefacta²¹⁹⁴.

Psychogenic excoriation (dermatotillomania): The patient induces skin damage by picking at areas that can be reached either because of sensations or a felt need to remove irregularities. Suggested treatments include doxepin, SSRIs, clomipramine, antipsychotics, naltrexone, and behaviour therapy.

Delusional parasitosis: The patient believes that the skin is infested with parasites. It typically affects females and people 40 or more years of age. (Sheppard ea, 1986, found an excess of males). It may be secondary to a variety of psychiatric illnesses or organic disorders (e.g. B12 deficiency, pellagra, and multiple sclerosis). It is difficult to treat. Supportive psychotherapy and pimozide (Orap) may help.

'*Dermatological non-disease*' (Meador, 1965): The absence of diagnosable symptoms and signs does not necessarily indicate an absence of significant problems. Symptoms are commonly confined to three areas: face, scalp and perineum. Facial burning, itching, and hairiness are common complaints. Scalp complaints include hair loss and irritation. Genital itch, redness, burning and discomfort are also common. The most frequent psychiatric diagnosis is depression. Other diagnoses include dementia and schizophrenia. Suicide and attempted suicide may occur.

Classification of patients with psychological/psychiatric problems attending skin clinic (Cotterill, 1989)

Depressed because of skin disease

Skin disease results from stress, strain or conflict (controversial)

Factitious disorders

Dermatological delusional disease (e.g. a physical complaint relating to skin/hair is common and most often related to depression)

Delusions of parasitosis (seen by dermatologists and environmental health officers)

Skin problems due to/exacerbated by psychotropics (e.g. lithium inducing acne or psoriasis*)

*Avoid tetracyclines in lithium-treated acne patients, but retinoids are allowed. Beta-blockers can exacerbate psoriasis. Both groups of drugs might exacerbate psoriasis by inhibiting cAMP formation.

Dermatological presentations of delusional disorder* (Munro, 1999)

Skin infestation (on and/or in/under skin)

Subcutaneous foreign bodies (eggs, seeds, minerals)

Bromosis²¹⁹⁵ (with/without hyperhidrosis)

Chronic cutaneous dysaesthesia²¹⁹⁶

*The patient may go to extreme lengths to remove 'objects'.

Hot flushes/flushes: The patient feels hot, there is cutaneous vasodilatation, and the core temperature drops subsequently. She may experience sweating, flushing, palpitations, anxiety (even panic), and irritability. Females may have nocturnal diaphoresis. Attacks usually last for a few minutes but may be longer or shorter than this, and the frequency of episodes varies enormously. Risk factors include low oestrogen levels (e.g. perimenopausal), low body weight, lack of exercise, and cigarette smoking.

Causes of hot flushes

Perimenopause

Systemic disorders e.g. pancreatic cancer, carcinoid syndrome

Neurological e.g. anxiety, migraine, cerebral neoplasia, spinal cord lesions, Parkinson's disease

Alcohol/drugs e.g. chlorpropamide, metronidazole, nicotinic acid, bromocriptine

²¹⁹³ Gardner-Diamond syndrome. Some authors believe that most cases are factitious. (Arnold, 2007, p. 248)

²¹⁹⁴ One theory was that there was sensitisation to own red cells after injury.

²¹⁹⁵ Delusion of smell emission.

²¹⁹⁶ Abnormal skin sensations +/- glossodynia or vulvodinia: may be more often related to personality disorder, anxiety disorder, or OCD.

Eating/food additives e.g. dumping syndrome, hot drinks, monosodium glutamate

Treatments include oestrogen, progestagen, and SSRIs. (Loprinzi et al, 2000; Stearns et al, 2002; Stearns et al, 2003)

General: Imipramine was discovered in the search for antihistamines. TCAs reduce skin blood flow, skin temperature, and sweating (they can also increase sweating). They are also sedatives, antiemetics, muscle relaxants and local anaesthetics. They are often effective in a variety of skin disorders (such as chronic urticaria, nocturnal pruritus in atopic eczema, etc.) and neurological disorders (e.g. postherpetic neuralgia, pain of diabetic neuropathy, unilateral itch after strokes, etc.). These facts hold irrespective of the affective status of the patient. TCAs and other newer antidepressants may reduce pain by causing an increase in noradrenaline and 5-HT that in turn inhibits nociception in the dorsal horn of the spinal cord. Gabapentin is effective also for postherpetic neuralgia (and for diabetic neuropathy) and it may be more efficacious for neuropathic pain if combined with nortriptyline. (Gilron et al, 2009) Mexiletine, a lidocaine-like drug, is sometimes effective for neuropathic pains, including that associated with diabetes, but GIT side effects may limit tolerability; patients with cutaneous hyperpathia may be helped by topical lidocaine. (Rowbotham et al, 1995) Pregabalin (Lyrica) is used as adjunctive therapy for partial seizures and for neuropathic pain of diverse aetiologies.

Psychogenic pruritus

Aetiology²¹⁹⁷ may be metabolic (e.g. icterus) or psychogenic

May be local or general

Scratching may excoriate skin

Depression and anxiety are common; chronic cases may be associated with repressed hostility/self-damaging behaviour with rise in tension that is relieved transiently by attacking skin

SSRIs, TCAs (H1-blockade), token economy, and aversion techniques may help

Chronic scratching may cause special forms of pruritic disorder: neurotic/psychogenic excoriation²¹⁹⁸, chronic lichen simplex²¹⁹⁹, and prurigo nodularis²²⁰⁰

Atopic dermatitis

Aim is to stop vicious circle of pruritus and scratching

Non-drug approaches: relaxation, habit reversal, stress management, CBT

Drug treatment (histamine antagonism): doxepin 5% cream, trimipramine²²⁰¹

Adrenergic urticaria

Emotional distress leads to acute onset of urticaria

Increased levels of adrenaline and noradrenaline

Treat with beta-blockers

Psoriasis

Highly heritable

Certain factors appear strongly associated with psoriasis: alcohol, smoking, exposure to streptococci, trauma, drugs such as lithium, beta-blockers and antimalarials²²⁰², and emotional stress (Williams, 1994)

Depression, subjective health and perceived stigma are stronger determinants of disability than are aspects of the disease (e.g. Richards et al, 2001)

Porphyria cutanea tarda

²¹⁹⁷ **Itching**

- Psychogenic* – psychiatric disorders, e.g. delusional parasitosis
- Pruritoceptive* – due to skin changes such as dryness or inflammation
- Neuropathic* – lesion of sensory pathways, e.g. MS, spinal neoplasms, post-herpetic
- Neurogenic* – arising centrally, e.g. cholestasis. Cholestatic pruritus is due to neuropeptide action on opioid receptors. (Wiesner et al, 2007)

²¹⁹⁸ Compulsive, ritualistic picking/digging into skin, often secondary to acne; groups of reachable lesions of same shape and size; crusts and scars (often white with pigmentation around edges).

²¹⁹⁹ Repetitive, pleasurable scratching leads to thick plaque with accentuated dermal lines in various parts of the body; interventions include occlusion, steroids, naltrexone, CBT, and habit reversal training.

²²⁰⁰ Hard, irregular, nodular limb lesions.

²²⁰¹ Trimipramine (50 mg/day) reduces sleep fragmentation and duration of stage I sleep.

²²⁰² Also, withdrawal of systemic or potent local corticosteroids can exacerbate psoriasis.

Alcohol abuse is important in aetiology

There is also a genetic element

Bullae on face, back of the neck, and dorsum of hands, and scarring

Discoid eczema²²⁰³

May be associated with alcohol excess in young males

Alopecia areata

Cutaneous T cell-dependent autoimmune disorder occurring in genetically susceptible individuals

Excess of exit (e.g. divorce), social (desirable or otherwise) and uncontrolled events during 6 months before onset

TCA's (e.g. imipramine 75 mg/day) may help hair growth independent of any influence on anxiety or depression

SSRIs helped in people with comorbid depression and anxiety

Psychotherapy and relaxation therapy may help

Acanthosis nigricans²²⁰⁴

Often associated with obesity and regresses with weight loss

Vulval lichen sclerosis²²⁰⁵

This affects infants and children and may falsely suggest abuse

'Speed bumps'

Excoriations of skin found in chronic users of stimulant drugs

Teeth

May be abnormal in many disorders e.g. eating disorders (erosion), schizophrenia (caries), congenital porphyria (pink fluorescence)

Loose teeth may require removal/special protection pre-ECT

Dental appliances should be removed before ECT unless required to protect oral structures from injury

Drugs causing dry mouth²²⁰⁶ predispose to dental decay

Patients may go to many dentists with a delusional abnormal bite ('phantom bite syndrome') or 'facial pain' and undergo many procedures, including extractions, without relief (Munro, 1999)

They may even have delusions about their dentures (Mack, 1985)

Nails

Clubbing occurs in a number of circumstances, e.g. bronchial carcinoma in nicotine dependent individuals

Blue lunulae in Wilson's disease

Blue-black colouration of nails, often worse in summer, may be due to phenothiazines

Acquired melanonychia, a dark discolouration of all or some (e.g. the thumbs) nails due to drugs such as hydroxyurea, zidovudine, minocycline, cyclophosphamide, and doxorubicin

Brown nails in chronic renal disease

Yellow nails may occur with congenital lymphatic hypoplasia

Green nails may be caused by *Pseudomonas aeruginosa* infection, e.g. in gardeners

Fingernail hypoplasia may follow first trimester exposure to carbamazepine or valproate

'Habit-tic dystrophy', due to picking at proximal nail fold of thumb, causing a ladder of transverse ridges/furrows up centre of nail

Beau's lines²²⁰⁷ are due to a temporary arrest of growth, and may be associated with arrest of hair growth and subsequent fall (telogen effluvium)

Mees' lines are white lines across the nails due to arsenic, thallium, other heavy metals, or renal failure

Lithium may cause diffuse hair loss as well as altered skin texture and golden discoloration of distal nail plates

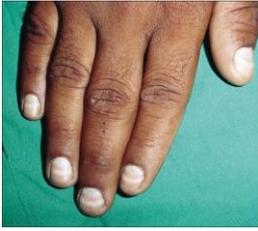
²²⁰³ A common form of eczema associated with coin-shaped limb lesions. Not confined to this age group. With many skin conditions it may be difficult to determine if skin problems, such as psoriasis, lead to drinking or *vice versa*.

²²⁰⁴ Velvety thickening and pigmentation of flexures occur. Also associated with primary (e.g. gastric) and metastatic malignancy (regresses with tumour excision) and with insulin resistance.

²²⁰⁵ The vulva is porcelain-white with purpura and scars.

²²⁰⁶ Xerostomia.

²²⁰⁷ Transverse lines related to acute physical or psychiatric illness or cytotoxic drugs.



Mees' lines

Patients with delusional parasitosis may tear away at their nails to get at subungal 'bugs'

Irritable bowel (colon) syndrome²²⁰⁸ (IBS)

Some proposed causes of this idiopathic disorder (Sibartie & O'Mahony, 2005)

Life stresses (especially if sustained)
 Exaggerated colonic response to CRF
 History of physical or sexual abuse²²⁰⁹
 Genetic factors (2 MZ to 1 DZ)
 Cognitive bias (emotional/physical symptoms = somatic disease)
 Reactions to infection²²¹⁰
 Altered gut motility
 Abnormally overactive gut-CNS interaction

Indicators suggestive of a disease other than IBS (Spiller, 2007)

Age > 50 years
 Male sex
 Short history
 Weight loss
 Night time symptoms
 Familial history of colonic cancer
 Bleeding per rectum
 Recent use of antibiotics

Lifetime diagnoses of depressive, somatoform, anxiety, panic and phobic disorders are increased. Creed ea (2005) looked at severe IBS and found that depressive, panic and neurasthenic disorders contribute to poor outcome. In fact, depression and depressive coping style are better at predicting subjective disability in IBD than is inflammation.(Cuntz ea, 1999) Common symptoms are diarrhoea, abdominal cramps, or alternating constipation and diarrhoea. Speed of onset is variable and the course is chronic and relapsing. Mucus may be found in large quantities in the stools. It is commoner in women in the West, and in men in India. It is a common bowel motility disorder that is non-inflammatory and often precipitated by stress. Sexual dysfunction has been reported be common. This might be due to spasm of the bowel causing pain during sexual intercourse. Mast cell number and secretions are increased in IBS.(Spiller, 2007) Psychotherapy,

²²⁰⁸ IBS can be diagnosed in the patient from pain/discomfort for the past year with 2 of (a) relief following defecation, (b) looser/more frequent stools, and (c) harder/less frequent stools. The relationship between IBS and psychiatric disorder is complex.

²²⁰⁹ An increased incidence of child sexual abuse has been reported in specialist clinics (see Drossman ea, 1995) but not in population-based studies.(Levenson, 2005, p. 298) Also, as pointed out by Guthrie (2007, p. 403) high rates of sexual abuse are reported in other chronic pain syndromes and are not specific to functional GIT disorders.

²²¹⁰ Patients with acute gastroenteritis who developed IBS-like features were found by Gwee ea (1996) to have higher scores (that persisted over 3 months) for anxiety, depression, somatisation, and neurotic traits, than those who did not develop these features. According to Gwee ea (1999) a third of cases of acute enteric infection develop IBS-like symptoms. Page and Wessely (2007, p. 130) point out that although prospective research suggested that more neurotic, anxious and depressed individuals are at increased risk for IBS following gastroenteritis such findings might only hold true in the rarefied atmosphere of the specialist clinic. Hamilton ea (2009) also found that gastroenteritis was a risk factor for IBS in general practice patients.

especially CBT (Mayer, 2008), may benefit those cases that fail to respond to medical measures²²¹¹, although the fact that a psychological approach helps does not prove psychogenesis. Also, Kennedy ea (2005) found that although CBT delivered by primary care nurses offered additional benefit over mebeverine the effect waned by twelve months. The evidence for CBT for IBS in primary care is at a 'preliminary' stage.(Moss-Morris, 2010) Gut directed hypnotherapy²²¹², although not readily available, may help severe cases.(Hayee & Forgacs, 2007) No drug controls all of the symptoms of IBS. TCAs have been found to help some IBS cases and SSRIs may improve more global symptoms.(Spiller, 2007) Low dose TCAs may be quickly effective which suggests that they may be acting as analgesics or anticholinergics²²¹³.(Creed & Olden, 2007, p. 65) Various drugs acting on the serotonergic system²²¹⁴ are being tried but controversy surrounds the possibility that they may be associated with ischaemic colitis, a condition that may be more common in IBS anyway.(Farthing, 2005) Spiller (2007) suggested trying 5-HT3 antagonists (e.g. alosetron) for global symptoms, diarrhoea, and pain, and 5-HT4 agonists (e.g. partial agonist tegaserod) for global symptoms, constipation, and bloating. However, the promise offered by the latter drugs do not seemed to have been fulfilled.(Fairclough & Silk, 2009, p. 312) Kaptchuk ea (2008) found that the positive effects of placebo treatment in IBS correlate best with the patient-practitioner relationship.

Adult²²¹⁵ acquired megacolon

It may be a symptom of depression or dementia, various neurological disorders, scleroderma, or hypothyroidism. It may be due to antidepressant medication or prolonged overuse of stimulant laxatives²²¹⁶ (e.g. senna).

Crohn's disease

Some cases have been mistakenly diagnosed as having anorexia nervosa. Genetic factors are important in this and ulcerative colitis. The risk for Crohn's disease is tripled in smokers (Palmer ea, 2006, p. 912 & 919) and the disease is exacerbated by smoking. The most effective intervention is to stop smoking. Ileostomies are associated with psychosexual problems, male infertility (surgery involving rectum), mechanical difficulties, dehydration (high ambient temperatures), and may be the site of disease recurrence.

Ulcerative colitis

Engel wrote about these patients' dependency needs and fear of failure and rejection during the 1950s. However, there are serious methodological flaws in much published research purporting to find a psychogenic basis for this disease. Chronic stress and depression might have a role in increasing the likelihood of relapse in both this disorder and in Crohn's disease. It is more common in non- and ex-smokers than in smokers.(Palmer ea, 2006, p. 912) Nicotine patches may reduce the intensity of flare ups.(Fairclough & Silk, 2009, p. 286)

Insulinoma²²¹⁷

Very rare episodic disorder, occur at all ages, and slight female preponderance
Usually benign adenomas in pancreatic islet cells, usually in body or tail of the pancreas
Some ectopic tumours near duodenum or porta hepatis
A small number are malignant (> 10%)
May be part of multiple endocrine neoplasia syndrome type 1 (MEN 1) with adenomas of other endocrine gland such as pituitary and parathyroid glands
Tumour may be present for years before correct diagnosis

²²¹¹ Reassurance, antispasmodics like mebeverine, high fibre diet, etc. Soluble fibre (ispaghula, sterculia) is a reasonable first choice. In a systematic review and meta-analysis, Ford ea (2008) found fibre, antispasmodics, and peppermint oil (antispasmodic) more effective than placebo.

²²¹² E.g. patient places hands over abdomen to induce a sense of warmth and comfort.

²²¹³ TCAs and SSRIs may worsen constipation and diarrhoea respectively in IBS.

²²¹⁴ E.g. cilansetron and tegaserod.

²²¹⁵ Children may develop acquired megacolon because they hold on to faeces.

²²¹⁶ Such laxatives cause degeneration of the myenteric plexus.

²²¹⁷ Some large sarcomatous tumours secrete insulin-like growth factor-1 with resultant hypoglycaemia.

Associated with diplopia, tremor, sweating, hunger, fatigue, weakness, dizziness, anxiety, palpitations, depression, agitation, confusion, loss of consciousness, grand mal seizures and, eventually, brain damage
 Memory for content of attacks is absent or hazy
 May be confused with personality disorder, panic attacks, depression, dissociative fugues, conversion disorder, epilepsy, or with alcoholic intoxication
 Blood sugar levels may be low or normal during acute attacks
 Whipple's triad: fasting/exercise induces symptoms²²¹⁸; hypoglycaemia (with inappropriately raised insulin levels²²¹⁹) during attacks; and symptoms respond to glucose
 Removal of the tumour is the ideal intervention but (if it evades detection or if the patient is old and only mildly affected) octreotide or another somatostatin analogue is useful

Peptic ulcer (PU)

During the 20th century the sex ratio for PUs changed from one of female to that of male predominance. PUs developed in Brady's 'executive monkeys' following electrical brain stimulation during the late 1950s. Monkeys who could avoid electric shocks by pressing a lever (having to make a decision) showed increased secretion of gastric acid and developed peptic ulceration more often than did monkeys who had no method of avoiding shocks. Studies on people with chronic gastric fistulae²²²⁰ have shown that emotional changes are paralleled by dynamic changes in the stomach. Anger led to a prolonged increase in gastric blood supply, whereas fear or sadness reduced gastric secretion, motility and blood flow. Alcohol and tobacco adversely affect the stomach and duodenum. Outdated psychodynamic theories stressed the aetiological role of oral gratification problems and subsequent proneness to excesses of rage. PUs may run in families. The role of acute stress in human populations is conflictual, although goal frustration has been reported before the onset of peptic ulcer. Creed (1992) reported no preceding excess of severe life events in straightforward peptic ulcer, but he did find an increase if the patient was psychiatrically ill. Stress and *Helicobacter pylori* may interact at times of upheaval, e.g. earthquakes. (Creed & Olden, 2007, p. 56) Magni ea (1986) found that the 16PF questionnaire divided 79 duodenal ulcer patients into three homogeneous subgroups: 32 dependent and anxious patients; 31 neurotic and anxious patients; and 16 patients with a 'balanced' personality. The authors felt that these findings upheld the concept of heterogeneity in peptic ulcer disease. In the 'balanced' group there was a non-significant increase in pepsinogen values. In a study by Walker ea (1988) serum pepsinogen correlated positively with increasing personality scores for hostility, irritability, and hypersensitivity. Some personality traits, such as hostility or dependency, may contribute to the pathogenesis of PU via increased smoking or alcohol intake. Subthreshold psychiatric disorders among PU patients impair quality of life and worsen prognosis. (Creed & Olden, 2007, p. 56) Alcoholism is very common among gastroenterology clinic attenders. Stress increases use of alcohol and tobacco. Indeed, nicotine-dependent and psychiatrically ill individuals consume 70% of all cigarettes smoked in the USA. (Grant ea, 2004) The exact role of alcohol (cause or exacerbation) is still debated. *Helicobacter pylori* infection only came into prominence in recent times. Antacids tend to reduce phenothiazine absorption by up to 45%. Interestingly, due to their strong antihistamine properties, trimipramine and doxepin have anti-peptic ulcer effects. Cholinesterase inhibitors increase gastric acid secretion, increasing the risk of bleeding in high-risk cases. SSRIs and venlafaxine increase the risk of GIT bleeding, especially in the presence of NSAIDs, and this risk is reduced by acid-suppressing agents. (de Abajo & Garcia-Rodriguez, 2008)

Non-ulcer dyspepsia

This consists of mainly stress-related symptoms: indigestion, wind, nausea, early satiety, and heartburn. There is no ulcer. Nocturnal pain is unusual and antacids are ineffective. Pain is diffuse, not of a recognised pattern, it is long lasting, is unaffected by food or fasting, and vomiting has no influence. Over-investigation should be avoided, particularly in young people. Treatment is by reassurance. Metoclopramide may help some cases.

²²¹⁸ It should be noted that propranolol can cause hypoglycaemia in non-insulinoma cases that are fasting or undertake vigorous exercise.

²²¹⁹ This was not one of Alan Oldfather Whipple's (1881-1963, US surgeon) original criteria for insulinoma.

²²²⁰ E.g. Beaumont's observations of Alexis St Martin (gunshot wound) in the 1830s and Harold and Stewart Wolff's observations of 'Tom' (their laboratory assistant) in the 1940s. Engel studied the infant Monica.

Burning mouth syndrome

Patients complain of a burning sensation in the tongue or other parts of the mouth, typically being absent on waking but increasing as the day goes on. There may also be complaints of dryness and altered taste sensation. There is usually no abnormal clinical or laboratory finding. Females, especially postmenopausal, outnumber males. Suggested treatments include vitamins, benzodiazepines, tricyclic antidepressants, anticonvulsants, topical capsaicin, and CBT.

Vomiting

A psychiatrist may occasionally be asked to give an opinion in a case of vomiting.

Aetiology of emesis

Gastrointestinal ('functional', inflammatory, obstructive)

Non-gastrointestinal (e.g. psychogenic, drugs²²²¹, radiation, migrainous, increased intracranial pressure, motion, pregnancy, infective, metabolic)

Important brain centres involved in vomiting are the chemoreceptor trigger zone²²²² and the (controversial) vomiting centre²²²³. Psychogenic emesis (or that due to pyloric canal ulceration) tends to occur whilst eating or just after a meal, whereas organic gastrointestinal disorders usually cause delayed postprandial vomiting.

Early morning vomiting associated with

Pregnancy

Metabolic disorders (e.g. renal failure)

Gastric surgery (may contain bile)

Alcohol consumption

Projectile vomiting (effortless, forceful, without retching) associated with

Pyloric stenosis

Increased intracranial pressure

There may be altered blood in the vomitus (coffee grounds). Undigested food suggests a pharyngeal or oesophageal problem. Distal obstruction may be associated with faecal vomiting. There may be abdominal distension or a succussion splash when the stomach is not emptying. Visible peristalsis denotes obstruction. 'Psychogenic vomiting' covers a multitude, e.g. eating disorders, factitious disorder, and stress-related (e.g. school examinations). Serum aldolase may be elevated in ipecac abusers.

Cyclical vomiting

Syndrome in young children

Idiopathic recurrent attacks of vomiting of widely varied frequency that may last for days

May have headache, abdominal pain, or fever

Most children 'grow out of it'

Post-prandial cholecystokinin levels can be relatively blunted in bulimics, and active purging may cause metabolic alkalosis (with raised bicarbonate), hypochloraemia, and hypokalaemia. Serum amylase levels may be raised due to chronic vomiting. Ipecac raises serum aldolase levels. Chronic laxative abuse may present as hypocalcaemia.

²²²¹ Tardive dyskinesia-related oesophageal dysmotility can cause emesis and weight loss.

²²²² Floor of fourth ventricle within the vascular appendage called the *area postrema*.

²²²³ Medullary lateral reticular formation.

Diarrhoea

Rahman ea,(2004) looking at a rural community in Pakistan, found that maternal depression before and after parturition predicted poorer growth and higher risk of diarrhoea in their infants.

Stomas

A distorted body image or *paraschemazia* may be due to hallucinogens, epilepsy, migraine, a stoma or amputation of part of the body. In addition, ostomies may cause occupational, dietary, and sexual difficulties as well as low self confidence and respect, disgust and shock.(Guthrie, 2007, p. 407)

Lung diseases

Chronic hypercapnia

This may cause problems sleeping, memory disturbance, diurnal drowsiness, lack of coordination, tremor, asterixis, myoclonus, and change in personality.

Pulmonary hypertension

There are many causes of pulmonary hypertension, the most common being COPD. However, of direct interest to psychiatrists are those cases caused by appetite suppressing drugs and talc inhaled with cocaine.

Chronic obstructive pulmonary disease (COPD)

The classical history is of smoking in excess of 20 pack years²²²⁴. Breathing retraining and CBT have been proposed as useful interventions for subjective distress. Propranolol causes bronchospasm. Sertraline possibly relieves dyspnoea to some extent (Smoller ea, 1998) and fluoxetine appears to be safe. Benzodiazepine (BZD) drugs cause respiratory depression. Short-acting BZDs, zolpidem and buspirone²²²⁵ particularly the latter two drugs are relatively safe.

Asthma

Asthmatics often have a personal or family history of hay fever or infantile eczema. There is evidence for a psychological element in asthma. Asthmatics may be particularly prone to a variety of comorbid anxiety and affective disorders.(Goodwin ea, 2003, 2004) However, proving direction of causality may be a problem: an asthmatic attack or the threat of such an attack is a frightening experience. The threat of infection with the plant pathogen *Burkholderia cepacia* has led to the breakup of self-help groups with resultant distress.

Precipitants of asthma attacks

Allergies, e.g. pet animals, pollen, dust, *Dermatophagoides pteronyssinus*²²²⁶

Cold air

Emotional problems²²²⁷

Dust/vapour/fumes/pollutants, e.g. cigarette smoke, strong perfumes, ozone, sulphur dioxide

Occupational exposure, e.g. glutaraldehyde, nickel, and manufacture of 'biological' washing powders

Physical exertion

Respiratory infection

Medication – beta-blockers and NSAIDs

Anticholinergic drugs (e.g. tricyclic antidepressants [TCAs]) dry bronchial secretions which may have implications for asthma sufferers. Panic disorder may mimic asthma and lead to the inappropriate prescription of bronchodilators.²²²⁸

Adrenaline (epinephrine) stimulates both alpha- and beta-adrenergic receptors. Orthostatic hypotension²²²⁹ due to antipsychotic drugs results from alpha-adrenergic blockade and giving adrenaline will only stimulate

²²²⁴ 1 pack year = 20 cigarettes/day for 1 year.

²²²⁵ Buspar was withdrawn, December 2009.

²²²⁶ The house-dust mite.

²²²⁷ The classic situation is the individual who was allergic to rose pollen but who also had asthmatic attacks when presented with an artificial rose.

²²²⁸ Interestingly, due to their strong antihistamine properties, trimipramine and doxepin have anti-allergy effects.

²²²⁹ **Orthostatic/postural hypotension** is defined as drop in blood pressure of > 20 or > 10 mmHg systolic or diastolic pressure respectively on standing from supine. Causes include prolonged bed rest, reduced extracellular volume (e.g. haemorrhage, burns, GIT

beta-adrenergic receptors leading to a further fall in blood pressure, a point to keep in mind if considering the use of adrenaline in acute asthma. Even 'selective' (beta-1) blockers such as atenolol may induce asthmatic attacks.

Lung cancer

This is the commonest cancer killer in Ireland (1 and 5 year survival = 23.7% and 8.6% respectively) and such deaths in women are catching up on breast cancer deaths.(Brennan ea, 2008) Lung cancer is the third most common cancer in both sexes in Ireland. The role of smoking in the genesis of lung cancer is incontestable.

Cystic fibrosis²²³⁰ (CF)

Patients with CF are living longer than before. Most men with CF are infertile²²³¹.(Chotirmall ea, 2009) Women tend to be subfertile, probably because the cervical mucus is abnormal, and pregnancy may be complicated. Parents need expert counselling. There are societies for interested parties and patients. Many affected children are small for their age and enter puberty late. Older children often become rebellious and need encouragement to continue with physiotherapy and medication. Adolescents may develop eating disorders. Educational abilities are normal in most cases. They can do most types of work except heavy manual labour. Those unfit for work need the help of a social worker. The finding of *Pseudomonas cepacia*²²³² in sputum of CF cases unhelpfully led to the admonition that such patients avoid one another. This led to the break up of self-help and educational groups with understandable distress.

Psychiatric contraindications to lung transplants (Coffman & Levenson, 2007, p. 42)

- Active alcoholism, drug abuse, smoking
- Severe mental disorder
- Treatment non-adherence

Drug interactions in the pulmonary patient

The anti-TB drug rifampicin, metabolised via P450 3A4, may compete with TCAs, SSRIs, bupropion, trazodone, and venlafaxine and compete through the same site with benzodiazepines, zolpidem, haloperidol, tiagabine, valproate, and carbamazepine. The leukotriene receptor antagonist montelukast²²³³ (Singulair) is metabolised via 3A4 and 2C9 and may lead to similar interactions to those associated with rifampicin.

Smoking, unlike nicotine gum, reduces theophylline levels by at least 50% and alcohol reduces theophylline clearance by almost a third. Prolonged seizures may occur if theophylline is given with ECT.

Multiple allergies

Some people believe that they are allergic to many things when this cannot be borne out objectively. A wide variety of psychiatric disorders have been reported in such cases. Arrogant confrontation has no place in management. Any underlying condition should receive attention. Encouragement to return to active living and discouragement of social withdrawal and disability are the mainstays of management.

Cancer

Adjustment disorder is the commonest psychiatric difficulty experienced by cancer patients. Excessive stress and a sense of helplessness have been postulated, but not proven, to promote cancer growth. It was generally held that relapse was more likely in breast cancer patients in the presence of severely threatening life events and difficulties, but a prospective study did not bear this out.(Graham ea, 2002) One systematic review (Petticrew ea, 2002) found that coping styles had no consistent effect on survival or recurrence in cancer patients.

losses such as vomiting or ileus, kidney losses such as diuretic drugs or analgesic nephropathy), drug-induced failure of peripheral vasoconstriction (e.g. alpha-adrenergic or calcium channel blockers, and nitrates), autonomic failure (e.g. diabetes mellitus and old age), and vasodilatation in septicaemia. Plasma is lost in such circumstances as peritonitis and burns.

²²³⁰ About 1 in 2,000 babies born in Britain have CF. It is the commonest lethal inheritable disease of Caucasians (autosomal recessive).

²²³¹ Atresia of vas deferens and epididymis.

²²³² A plant pathogen, often multiply resistant to antibiotics and associated with a rapid downhill course.

²²³³ E.g. used as add-on therapy for poorly controlled mild to moderate asthma.

Type C personality

Emotionally suppressed, compliant, conforming, stoical and unassertive
Suggested by Cull (1990) as being linked to cancer

It has been suggested that breast cancer may be particularly common in chronic psychiatric patients (Halbreich *et al.*, 1996) but the contribution of antipsychotic drugs to breast cancer, possibly by causing increased prolactin levels, is relatively small²²³⁴, if true. (Wang *et al.*, 2002) However, some research findings suggest a reduced likelihood of breast cancer in women with serious mental illness. (Bark *et al.*, 2008) Tumour growth rates may be accelerated in animals by uncontrollable stress. Chemotherapy and radiotherapy can cause cognitive and affective symptoms. Carcinoma of the lung (16% of cases), ovary and stomach can cause brain syndromes in the absence of metastases. Children educated about their cancers have good psychological outcomes if they happen to survive.

Despite undoubted medical progress, parents of children with leukaemia may have great difficulty accepting the diagnosis, the children often develop behaviour problems, and leukaemic children may feel that they have a foreshortened future. Diagnostic and therapeutic procedures, as well as frequent hospital admissions can be emotionally challenging. Cognitive problems are associated with irradiation of meninges and intrathecal methotrexate.

Psychological complaints in cancer patients

E.g. anxiety, depression, sexual problems, and fear of recurrence²²³⁵

Common

Often untreated

Lassitude is also a major difficulty

Patient may not inform doctor of such difficulties

Sexual problems include fear that pregnancy will spread the cancer or that the baby will be abnormal

May fear spreading disease to healthy partner

Fear of being repulsive because of body image or unpleasant smells

Guilt may follow avoidance of sexual activity

Continued sexual activity is important and helps in coping with hopelessness

Loss of hair from therapy causes embarrassment

Patients should be referred for hairpiece fitting before hair loss starts

Family is greatly affected by cancer

Graded use of photographs and other preparatory measures help people facing surgery to adapt to the aftermath

Depression is more common after breast cancer with:

- Past psychiatric history
- Treatment toxicity
- Lymphoedema
- Pain
- Body image problems
- Lack of a confidant
- Low self esteem
- Unresolved concerns

²²³⁴ 14% chance of getting it from the drug.

²²³⁵ Fear of recurrence was the main concern in Canadians who had been treated for cancer at least 6 months before the study: 42% admitted to this concern. (Charles *et al.*, 1996) Patients may be embarrassed by symptoms (e.g. unpredictable diarrhoea) and this may lead to anticipatory anxiety/agoraphobia. According to Massie (2004) rates of depression vary with cancer type: oropharynx (22-57%), pancreas (33-50%), and lung (11-44%) have high rates; lower rates are associated with colon (13-25%) and lymphoma (8-19%).

Depression in cancer patients should not be dismissed as 'expected' or 'understandable' – it should be treated appropriately with psychotherapy and/or medication. Venlafaxine may help reduce hot flushes in survivors of breast cancer,(Loprinzi ea, 2000) as may citalopram and paroxetine. Mirtazapine reduces physical symptoms such as pain, nausea and anorexia.(Sherman & Fisch, 2004) Depression secondary to interferon-alpha can be prevented or treated by SSRIs such as paroxetine²²³⁶.(Musselman ea, 2001) In a study employing a patient-completed questionnaire,(Frost ea, 2000) most American women who underwent bilateral mastectomy as a prophylactic measure because of a strong family history of mammary carcinoma were happy with the procedure, although a minority was dissatisfied with bodily appearance. Some felt less emotionally stable, felt more stressed with reduced self-esteem, had unsatisfactory sex lives and felt less feminine. In other work, women who regretted prophylactic mastectomy felt that the decision to operate had come from the surgeon.(Payne ea, 2000)

Gynaecological cancer treatments may lead to sexual problems²²³⁷, but successful treatment may be complicated by psychosexual problems in the either partner, e.g. fear of transmitting or 'catching' cancer, problems from disfigurement, or attribution of cancer to past sexual activity. Such issues need airing before and after treatment.

Some anti-cancer drugs, especially the alkylating agents²²³⁸, can cause sterility that may be irreversible. In males, the storage of sperm should be considered when chemotherapy is given with curative intent.

Corticosteroids may induce manic symptoms, as rarely may diencephalic tumours.

Doctors may see themselves as 'tellers' or 'non-tellers'. They should, however, individualise information and find out what the patient is really asking. We cannot prognosticate accurately for individual patients. We should tell them that 'life may be short but its length remains uncertain'. The patient should be given the information requested but not bombarded with facts. There is some evidence that doctors may try to keep the patient alive or to cure cancer to too great an extent. There may be more pressing indications for a greater emphasis on the care and comfort of the terminal cancer patient, with more use of analgesics and psychoactive drugs and less use of radiotherapy and chemotherapy.

Imparting bad news

Problems in the doctor – untrained²²³⁹ (how and where to tell and how to answer questions), uncertain (of patient's reaction or if the therapeutic relationship will suffer), and unsure (if patient will be upset)

Preparation – consider patient's prior knowledge and supports/resources, likely questions and types of reaction and appropriate responses, knowledge of patient's previous responses to adversity

When to tell – this is based on a consideration of many issues, e.g. ensuring a safe journey home or the return of a next-of-kin from holidays

Who to tell – does the patient want a friend/relative present, consider capacity/minors/Wards of Court issues

Where to tell – privacy, seated patient and doctor

What to tell - ask what is/wished to be known, give information stepwise, gently make sure you are understood, be realistically hopeful

Arrange further appointment and share relevant information with those professionals who have to know

CBT may help cancer patients cope better if it is brief, problem-focused, and modified to meet individual need. Imagework,(Kearney, 1992) where the patient focuses on mental images in his mind and asks himself questions that allegedly helps him to work through repressed material, has been advocated for pain, including cancer pain, that is inadequately responsive to physical interventions and which is considered to have a significant emotional component. Denial is not confronted during this procedure.

About one in four patients receiving combined chemotherapy develop nausea and vomiting if reminded of the treatment (Watson ea, 1992) and this response may lead to treatment avoidance. The newer antiemetic drugs like ondansetron are of help here. Also, infusions may be covered with an anxiolytic, e.g. lorazepam 2 mg T.I.D. for 48 hours before and during therapy. Tamoxifen may reduce TCA serum levels and thus interfere with the therapeutic efficacy of these antidepressants; and induced menopause (surgical,

²²³⁶ Interferon causes fatigue, neurocognitive dysfunction, and various degrees of depression.

²²³⁷ Loss of vagina, or radiotherapy damage to sacral nerves.

²²³⁸ Muscarine, cyclophosphamide, chlorambucil, etc.

²²³⁹ Delegation of this duty to the most junior member of the team is unacceptable.

tamoxifen) may lead to vasomotor symptoms. Also, SSRI antidepressants may reduce blood levels of tamoxifen metabolites and their use in women taking tamoxifen for breast cancer has therefore been questioned. (Jin et al, 2005) The combination of paroxetine and tamoxifen may worsen prognosis in breast cancer patients. (Kelly et al, 2010)

Paraneoplastic syndromes (PS) involving nervous system

PS (Darnell & Posner, 2003) refers to symptoms or signs due to organ or tissue damage at sites remote from primary or secondary neoplasia. There are many such syndromes, e.g. hypercalcaemia, Cushing's syndrome, and wasting. Most PS is due to tumour-derived substances that mimic normal hormones or interfere with circulating proteins. One²²⁴⁰ or many²²⁴¹ parts of the nervous system may be involved. A single cell type, such as cerebellar Purkinje cell, may be affected. Involvement of the spinal cord can lead to various inflammatory disorders, stiff person syndrome, amyotrophic lateral sclerosis, or sensory (dorsal root) neuropathy.

Other potentially affected areas

Peripheral nerve - various neuropathies

Neuromuscular junction - Lambert-Eaton myasthenic syndrome²²⁴², myasthenia gravis

Muscle - polymyositis, dermatomyositis, necrotising myopathy, myotonia

Neurological disorder usually precedes overt malignancy by months, even years. Many patients have serum and CSF antibodies that react with nervous tissue and the neoplasm.²²⁴³ Underlying pathology varies widely.

Spinal cord injury

Migliorini et al (2008) examined mental health status in cross-section among 443 community-based adults with injured spinal cords. 48.5% had mental health problems (over twice the general population rate) and 60% had more than one problem. 37% were depressed, 30% were anxious, 25% were clinically distressed, and 8.4% had PTSD.

Most patients with spinal cord injury fail to ejaculate, or if they do, it is either non-orgasmic or with only an awareness of some altered feeling. Most male paraplegics with spinal cord injury put resumption of sexual function at the top of their wish list. Patients with spinal cord injury often say that they develop an area of arousal lying superior to the level of the lesion leading to sexual satisfaction ('phantom orgasm') from tactile experiences such as caressing.

Sensory deprivation follows acute high cervical cord injury. This is due to lack of sensory information from the environment and from immobilisation. This may lead to apathy that can be misconstrued for depression. Also, steroids may be used to reduce cord oedema. It is better to observe such cases for about four weeks than to rush in with antidepressants.

The spinal cord-injured patient who still feels (but does not believe) as if he/she is in/on the vehicle in which the trauma occurred may think he is losing his mind. He/she needs to be reassured that such persisting perceptions are a recognised complication of cord injury.

Vermiform appendicitis

Patients with a normal appendix at laparotomy have been found to have experienced more severely threatening life events in the weeks before the onset of abdominal pain than did those found to have an acutely inflamed appendix. (Creed, 1981) Similarly, severe life events or chronic problems may be associated with so-called functional acute abdomens of other varieties. Patients with a normal appendix at laparotomy are at increased risk of future hospital visits, particularly for self harm and for being seen by the liaison psychiatrist. (Dummett et al, 2002) Schizophrenic patients tend to have raised pain thresholds and may

²²⁴⁰ E.g. limbic encephalitis (amnesia, dementia, seizures; CSF raised protein and pleocytosis; anti-Hu antibodies), brainstem encephalitis, cerebellar degeneration, optic neuritis, retinopathy, Parkinsonism, chorea.

²²⁴¹ E.g. encephalomyeloradiculitis.

²²⁴² Eaton-Lambert syndrome: Myopathy of cancer (small-cell carcinoma of lung) or thyrotoxicosis with myasthenic-like syndrome but, unlike myasthenia gravis, there is no response to IV edrophonium chloride (Tensilon). Anti-calcium channel antibodies are found.

²²⁴³ For example, Anti-Ma1 antibody reacting with neurones and, for example, lung cancer, and associated with brainstem encephalitis and cerebellar degeneration.

sometimes not complain of pain with acute appendicitis, perforated peptic ulcer, MI, or other serious medical events.(Dworkin, 1994; Marchand, 1955)

Amputation

Surgeons have traditionally delayed surgery for chronic disorders so that people might feel sufficiently relieved after intervention that they put up with the inconvenience caused by surgery. Amputation may be an acute or planned event. Those amputees who realistically appraise their situation and who work hard with rehabilitative measures do best. Late onset phantom limb pain may indicate a depressive illness. It seems to take some amputees many months before they appear as such in their dreams, although the dream content and changes therein varies widely between individuals.

Phantom and supernumerary limbs

Experience of possessing a limb that does not exist - in the first case the limb was amputated whereas in the second instance an extra limb is experienced

Phantom limb

Described in 1649 by Ambrose Paré

Tactile (often painful) rather than visual phenomenon, usually disappearing a matter of days after amputation²²⁴⁴

Usually the 'limb' is 'absorbed' or telescoped into the body, although some patients have a permanent phantom

Very young children rarely experience phantoms

Congenital limb absence may occasionally be associated with replacement phantoms

Preoperative anaesthetic block does not reduce the likelihood of phantom limb pain (Bach ea, 1988; Birbaumer ea, 1997; Flor, 2002)

Supernumerary limb

Experiencing an extra hand, fingers or limb, the number and site of such extra parts varies between patients

May occur with anosognosia for a left-sided hemiplegia

Usually there is retained insight

Looking at the limb may cause the extra part/phantom to disappear

Disorders of body schema

Abnormal awareness of spatial characteristics of the person's own body

Partially paralysed limb may feel excessively heavy or large (*hyperschemazia*) – found in multiple sclerosis, vascular disease, spinal cord lesions, toxic states, conversion states, hypochondriasis, dreaming, and in states of depersonalisation

Aschemazia and *hyposchemazia* (part of body seems smaller or absent respectively) may occur when the cord is divided, with parietal lobe lesions (e.g. right middle cerebral artery thrombosis), or in depersonalised states or in healthy people who are under water

Paraschemazia (distorted body image) can be due to hallucinogenic drugs, epilepsy, migraine, with a colostomy, or following amputation of a body part; however, rare cases of amputation-seeking people tend to say that they experienced a mismatch between anatomy and the self before amputation and to feel very well follow the procedure (First, 2005)

Strokes²²⁴⁵

CT is better than SPECT in distinguishing between haemorrhagic and non-haemorrhagic stroke. Overall, 20-40% of patients develop depression in the months following a CVA, and about half of these have major depression with the remainder suffering less severe (minor) depression.(Robinson, 2000) House ea (1991)

²²⁴⁴ Similar phenomena may follow nerve plexus, thalamic, or brainstem lesions. Breast, eye, or genital phantoms may follow removal of the relevant organs.

²²⁴⁵ Eventual level of **functioning achieved after a CVA/stroke** depends on many interconnected factors, e.g. amount and area of brain damage, quality of remaining brain tissue (CVA may unmask underlying Alzheimer disease), specific organic deficits (dysphasia, hemianopia, etc), psychological adjustment, length of immediate confusional state, extracerebral complications (e.g. cardiac failure), support offered by family and society, and facilities available for assessment and rehabilitation.

found a high post-stroke cumulative incidence of psychiatric disorders, but little of this persisted. However, Morris *et al.* (1993) found that depression following CVA was associated with greater mortality (particularly if accompanied by social isolation). Other workers have confirmed this finding. Various polymorphisms of the serotonin transporter gene (SERT) may be associated with post-CVA depression. (Kohen *et al.*, 2008) Various associations have been suggested between the site of a cerebrovascular lesion and psychiatric disorder, e.g. depression/left hemisphere (especially anterior/basal ganglia: Vataja *et al.*, 2001), mania/right hemisphere (especially limbic-connected and thalamus), and bipolar/right basal ganglia or thalamus. Robinson (2003, p. 730) argues that the association of post-stroke depression with proximity to the left anterior lobar pole and left basal ganglia may be an acute phenomenon, i.e. holding true in the first 1 to 2 months after a cerebrovascular accident.

Antidepressants, especially SSRIs, can be used to treat or prevent post-stroke depression and they may improve cerebral recovery and improve long-term survival. Executive dysfunction is common after stroke, an outcome that may be ameliorated by antidepressant drug therapy. (Narushima *et al.*, 2007) Antidepressants may be augmented with calcium channel blockers in post-stroke depression.

Psychostimulants, such as methylphenidate, are sometimes used to treat post-CVA depression, especially in the USA. (Lazarus *et al.*, 1994)

Anxiety is common post-CVA. Understandably, many patients are worried lest they develop further strokes (e.g. during sexual activity). Agoraphobia and misinterpretation of anxiety symptoms as premonitory symptoms of CVA may follow. OCD symptoms may follow CNS infarction, especially one involving the basal ganglia.

Emotional lability (emotionalism) can occur early or late in the history of stroke and it may respond to SSRIs or TCAs. (Robinson *et al.*, 1993) Laughing or crying occurs with no relation to internal mental state. The term 'silent' infarct means different things to different people. The infarct is either so small or in an area of brain that allows its effects to go unnoticed. It could mean that there are no discernible physical signs (see strategic infarct in box). However, such cases can be psychiatrically 'noisy' and present in a manner ranging from delirium to a pseudo-'functional' psychosis²²⁴⁶. MRI population-based work from Rotterdam (Vermeer *et al.*, 2003) suggests that these cases are at increased risk for dementia.

Strategic infarction

Unexpectedly severe cognitive impairment (dementia +/- specific signs such as paralysis) following an infarction in certain 'strategic' areas:

- Inferior genu of internal capsule
- (Medial) thalamus
- Left angular gyrus (with Gerstmann's syndrome)
- Basal ganglia
- Basal forebrain
- Area supplied by posterior cerebral artery

MELAS syndrome

Rare maternally inherited mitochondrial encephalopathy

Lactic acidosis and stroke-like episodes

Usually seen in children

May present in adults with migrainous headaches, deafness, stroke-like episodes, and a progressive dementia (Clark *et al.*, 1996)

Concerns have been raised concerning an association between the cough cure agent phenylpropanolamine and CVA in young women. Higher doses used in America and methodological flaws may have partly led to this finding. Phenylpropanolamine should be avoided in certain circumstances, e.g. acute cardiac ischaemia, hypertension, hypotensive therapy, MAOIs, anticholinergic therapy, and phenothiazine therapy.

²²⁴⁶ The prevalence of psychosis specifically due to stroke is low and may be more common with right-sided lesions. (Bourgeois, 2007)

SSRIs are the drug treatment of first choice for depression following stroke, except for haemorrhagic stroke (risk of bleeding: Robinson, 2000). A meta-analysis (Antithrombotic Trialists' Collaboration, 2002) found low dose (75-150 mg/day) aspirin reduced the risk of vascular events (at least 150 mg/day in acute setting) but that adding dipyridamole to aspirin did not significantly improve outcome. Blass and Ratan (2003) appear to disagree.

Olanzapine and aripiprazole are 'contraindicated' in elderly patients with dementia-related psychosis and/or behavioural disturbance because of evidence for an association with an increased mortality rate and a greater likelihood of stroke. Similar concerns have been raised for risperidone²²⁴⁷ and other atypical agents. One UK GP database study suggests that the risk of stroke is increased with *all* antipsychotics, more so for atypical drugs than for typical agents, and more so for dementia patients than for those without dementia.(Douglas & Smeeth, 2008) However, decisions need to be based on a case by case basis. Also, there is also evidence against an association between stroke and atypicals in elderly subjects with dementia!(Gill ea, 2005)

Active and passive smoking are risk factors for stroke.(Bonita ea, 1999) as may be hormone replacement therapy in postmenopausal women.(Bath & Gray, 2005) Eating fruit and vegetables reduces the risk of stroke.(He ea, 2006) possibly by supplying potassium, folate, fibre, and antioxidants like ascorbic acid, flavonoids, and betacarotene.

Deafness²²⁴⁸

At least one in seven people have some loss of hearing²²⁴⁹, one in every thousand being very deaf from early life.(Du Feu, 2010) Hysterical deafness is rare, accounting for 4% of hysteria cases in an American series in the early 1960s. People who are born deaf have no increase in psychiatric illness, although they may be prone to behaviour problems. The latter may stem from parental over-protection, separation in institutions, adverse reactions of third parties, excess emphasis in teaching on speech at the expense of sign language, or associated brain damage. Deaf children of deaf parents do particularly well. Intellectual disabilities are commonly associated with deafness. Desensitisation to wearing a hearing aid may be needed. High frequency hearing loss is common in early middle age in Down's syndrome patients and may account for apparent deterioration in cooperativeness. Whilst persecutory states are the classical psychiatric problem in the elderly with hearing impairment depression is more common in practice. Also, because hearing impairment is so common in the elderly, no accurate deduction about a role for deafness in psychiatric disorders can be reached with using a matched control group.(Gloag, 1980) There is cross-sectional evidence that high ambient noise, as when schools are close to airports, can affect cognitive development in children, specifically reading comprehension.(Stansfeld ea, 2005)

Tinnitus

'Phantom auditory sensation without an acoustic generator'²²⁵⁰ is common and often chronic. Tinnitus becomes more common with age. Onset may follow negative life events such as retirement, redundancy or divorce. Over one-tenth of cases seen by specialists have good or reasonable hearing. About 5% of adults have their sleep regularly disturbed by buzzing or other noises in their ear(s). Affective disorder is a common accompaniment. IV lignocaine abolishes or ameliorates tinnitus. Management must be holistic and includes supportive psychotherapy, treatment of depression (nortriptyline has been recommended), tinnitus maskers, etc. It is important to distinguish tinnitus from crude auditory hallucinations, e.g. in schizophrenia. Objective tinnitus²²⁵¹ can be caused by such problems as tumours, arterial abnormalities,

²²⁴⁷ Risperidone is the only antipsychotic licensed in Ireland (for up to 6 weeks) for use in dementia if other approaches fail and following a risk-benefit analysis. Risk increases if risperidone is combined with furosemide.(Irish Medicines Board, 2009)

²²⁴⁸ Francisco Goya (Spanish, 1746-1828) may have become suddenly deaf from Harada's disease (retinal detachment plus deafness, a variant of Vogt-Koyanagi disease), a fact that might explain his change from painting happy and coloured pictures of attractive people to a much more pessimistic output, e.g. '*Saturn Devouring His Son*' (1819).

²²⁴⁹ Presbycusis, due to cochlear degeneration, is the most common cause of deafness. It is usually associated with ageing but chronic noise exposure is also implicated. Higher frequencies are most affected. Because consonants are high frequency sounds (vowels are the opposite) speech becomes difficult to decipher and using a hearing aid that increases volume only makes vowels louder ('Stop shouting. I'm not deaf!'). An aid that is specific for high frequencies is ideal.

²²⁵⁰ There may in fact be a generator, i.e. pathology like glomus tumour, carotid body tumour, or essential palatal myoclonus.(Walshe ea, 2002)

²²⁵¹ Tinnitus that is audible to examiner.

myoclonus, insects, temperomandibular joint abnormalities²²⁵², and a patulous Eustachian tube.(Walshe ea, 2002)

Ophthalmology²²⁵³

Environmental light appears to influence the time of onset of the menarche: completely blind girls reach menarche earlier than partially sighted girls, the latter achieving this developmental milestone before the normally sighted; and girls are more likely to have their first menstrual period during autumn/winter than during spring/summer.(Steiner ea, 2002)

Hypernyctohemeral (or non-24-hour-day) syndrome

Resembles normals in time-free environment

Common in totally blind people; some cases live isolated lives

Retires and rises to/from bed 45 minutes later each day

Sleep-wake cycle of 24.5-25 hours

Over about 21 days a cycle is completed

Management: morning bright light, vitamin B₁₂

Usher's syndrome²²⁵⁴ was said to be associated with schizophrenia in about 15% of cases.(Hallgren, 1959) William's syndrome²²⁵⁵ includes a stellate or starburst pattern in the iris. A cherry-red spot on fundoscopy may be found in Tay-Sachs disease²²⁵⁶ and in sialidosis.²²⁵⁷ The X-linked disorder oculocerebrorenal dystrophy (Lowe's syndrome)²²⁵⁸ consists of generalised aminoaciduria, abnormal skull shape, congenital cataracts, intellectual disability, and hypotonia. There is a Fanconi-type proximal renal tubulopathy. Nystagmus may be secondary to drugs such as BZDs or barbiturates. It must be distinguished from nystagmoid jerks, which are normal and occur when the examiner forces the patient to follow an object beyond the natural sweep of the eyes. Eyelid myoclonia with absences is an epileptic phenomenon wherein there is jerking of eyelids, the eyes may jerk upwards, and there is retropulsion of the head. Macular degeneration²²⁵⁹ is more likely to occur in smokers.(Mitchell ea, 2002; Kelly ea, 2004) Black-patch psychosis (delirium²²⁶⁰) may follow eye surgery where the eyes are covered for a prolonged period of time. Its occurrence may be greatly diminished by putting pinholes in the patches or by removing one patch at a time during recovery. A perception of the world as tilting has been found in people with a lateral medullary infarct. Upside-down reversal of vision, usually transient, results from posterior circulation ischaemia (e.g. vertebral artery dissection: Evans & Mathew, 2005, p. 259). Hallucinations in a blind visual field have been explained as release phenomena. The Charles Bonnet²²⁶¹ syndrome consists of poor sight and visual hallucinations. Other causes of 'positive' visual disturbances include migraine (e.g. fortification spectra), retinal damage such as detachment (phosphenes or simple flashes of light)²²⁶², drugs, epilepsy, and primary visual cortical lesions. Phosphodiesterase inhibitors may cause a following day green visual tinge.

²²⁵² Temperomandibular joint dysfunction is often viewed as a functional somatic syndrome. The use of splints in this disorder is not supported by the evidence.(Page & Wessely, 2007, p. 141)

²²⁵³ Grief in blind people, eye poking and tunnel vision are discussed in O'Shea. (2002)

²²⁵⁴ Early onset of deafness and blindness (retinitis pigmentosa), autosomal recessive, described in 1852 by Albrecht Von Graefe, and named for a British ophthalmologist Charles Usher.

²²⁵⁵ There is a deletion on chromosome 7, variable levels of intellectual disability between cases (verbal IQ may be high enough to be misleading), 'cocktail party speech' (loquaciousness) elfin facies, supraaortic stenosis, renal artery stenosis, hypertension, anxiety, and depression.

²²⁵⁶ *Tay-Sachs disease* is a sphingolipid storage disorder of infants with excessive startle response, extreme motor and cognitive delay, visual loss, spasticity, seizures and death before age 5 years.

²²⁵⁷ *Sialidosis* is a storage disorder with facial dysmorphism.

²²⁵⁸ A mutation is found in the gene OCRL1 at Xq26.1 which codes for phosphatidylinositol (4,5) biphosphate 5 phosphatase.

²²⁵⁹ The most common cause of blindness in developed countries according to Anonymous.(2008b) Failure of regulation of both classic and alternative pathways of complement activation appear to operate.

²²⁶⁰ Postoperative delirium is associated with being very old and heavy preoperative benzodiazepine use.(Inouye, 1998)

²²⁶¹ Charles Bonnet (1720-1793), Swiss naturalist, described this condition in his grandfather (Charles Lullin) who had bilateral cataracts and saw visions of people, birds, carriages, etc when he was almost 90 years old. Before Bonnet himself died (age 73 years), when he was almost blind, he developed the same syndrome himself!

²²⁶² Severe, early onset bilateral retinal disease (e.g. CMV retinitis) may cause the child to poke an eye to elicit visual sparks or *phosphenes*.

Cataract surgery performed with topical or regional anaesthesia is often associated with seeing light or colours (usually yellow and red) or (less commonly and clearly) aspects of the environment (e.g. a surgical instrument). This is frightening to a small minority of cases. Preoperative explanation and holding the patient's hand during cataract surgery appear to help. (Moon & Cho, 2001)

Oculogyric crises are dystonic reactions classically associated with encephalitis lethargic/post-encephalitic Parkinsonism, neurosyphilis and (particularly older/typical) antipsychotic drugs. However there are many other organic causes of this phenomenon, e.g. head injury, herpes encephalitis, MS, Tourette syndrome, infarcts of both thalami, lesions of fourth ventricle, cystic glioma of third ventricle, and juvenile Parkinson's disease. Reported iatrogenic causes include reserpine, lithium, carbamazepine, metoclopramide, TCAs, L-DOPA, nifedipine, chloroquine, and cisplatin. Cases have been recorded in patients taking (surprisingly) benzodiazepines and following influenza vaccination.

Conjunctivitis secondary to faecal contamination (ano-ocular spread by hand) is common in the behaviourally disturbed elderly. Dysthyroid eye disease (ophthalmic Grave's disease) is more common and more severe in people who smoke.

The drug of choice for depression in glaucoma patients is an SSRI. Avoid TCAs in narrow angle glaucoma, but they can be used in cases of open angle glaucoma. The actual situation is more complicated than these simple rules suggest. TCAs have sympathomimetic, anticholinergic, and sympatholytic (alpha-1-blocking) actions. Desipramine, despite weak anticholinergic effects, is likely to increase the risk of glaucoma because the balance of its effects causes mydriasis. However, amitriptyline, a powerful anticholinergic TCA, is unlikely to provoke glaucoma because it has little effect on pupil size because of the counterbalancing effect of sympatholysis.

Bitemporal hemianopia (outer half of each visual field affected²²⁶³) is usually due to tumours of, or near, the pituitary gland, whereas binasal hemianopia can be caused by calcified, expanding internal carotid arteries. Both are classified as heteronymous (crossed) hemianopias. Quadrantic hemianopia is due to a lesion of the optic radiation or, more rarely, the occipital lobe.

High dose thioridazine may cause

Pigmentary retinopathy (poor visual acuity, loss of peripheral vision, scotomata)

Chromatopsia (e.g. seeing yellow or red)

Pyrexia of 'unknown' origin²²⁶⁴ (PUO)

Psychiatrists are sometimes asked to evaluate a case of PUO. It is good practice to assume that something has been overlooked until proven otherwise, e.g. the present author has diagnosed tuberculosis in two cases presenting with respiratory symptoms and 'negative' work up by finding *M. tuberculosis* in gastric washings. A complete and chronological history is often revealing as is a review of those tests that have (and have not) been done.

²²⁶³ Compression of chiasma from underneath firstly affects lowest crossing fibres with resultant upper outer visual defects; bitemporal hemianopia follows with further field loss. A pituitary tumour can spread down into the sphenoid air space or, extremely rarely, the nose (CSF rhinorrhoea). Very rarely is there lateral spread to involve the cavernous sinuses (ophthalmoplegia from damage to oculomotor nerves).

²²⁶⁴ Historically there are childbed fever (the present author diagnosed infected retained placenta twenty years ago in a delirious patient transferred from a maternity to a psychiatric hospital) and the improvement of neurosyphilis with malaria treatment.

Fevers of particular psychiatric interest include those associated with pneumonia in a sedated patient, meningitis, fever in an antipsychotic drug-treated patient exposed to high ambient temperatures, delirium tremens, withdrawal from TCAs, cheese reactions (MAOI plus tyramine), MAOI plus pethidine reactions, eosinophilia-myalgia syndrome (contaminated l-tryptophan), benign low grade fever with clozapine or reaction to drugs like carbamazepine/oxcarbazepine/SSRIs/nefazodone, increased risk of lithium toxicity with pyrexia, fever from marrow suppression (clozapine, carbamazepine, etc), side effect of anticholinergic drugs, febrile convulsions (association with later epilepsy in some cases), precipitation of epileptic attacks by fever, improvement and worsening of restless legs syndrome and multiple sclerosis respectively with fever, depression following fevers such as brucellosis, lethal catatonia, neuroleptic malignant syndrome, NMDA, burst internal bag of cocaine, and factitious fever. (see also Ahuja & Cole, 2009) **Factitious fever** is suggested by normal appearance, absent diurnal rhythm, no change in pulse rate with temperature change, no sweating as temperature abates, very high temperature, normal ESR/CRP, self-harm/injection marks/paraphernalia, and tampering with thermometer.

People with eating disorders have an elevated state-dependent pain threshold. People with borderline personality disorder report lack of pain when cutting themselves.

Pain

Nociceptive pain – direct stimulation of peripheral nerve ending²²⁶⁶

*Neuropathic*²²⁶⁷ pain – abnormal pain perception in the peripheral or central nervous systems²²⁶⁸

Combined pain – nociceptive and neuropathic, e.g. bone secondaries

Asymbolia for pain - pain is recognised but does not upset the perceiver, follows damage to the anterior insular cortex

'Jurisgenic' pain - maintenance of the sick role with complaint of pain in order to maximise financial return

Depression and pain may have a reciprocal relationship. 5-HT and noradrenaline inhibit pain transmission from the dorsal horn of the spinal cord. A reduction in noradrenaline availability leads to pain and low mood. Antidepressants with relatively greater noradrenaline reuptake inhibition have better analgesic efficacy than are those that are more 5-HT selective. (Atkinson et al, 1999; Fishbain, 2003) Binding of substance P to neurokinin receptors, an increase in cytokine activity, or decreased opioid receptor activity lead to pain and depression.

Reduced activity for fear of pain leads to poor conditioning which leads in turn to more discomfort if activity is undertaken.

Gate theory of pain

This starts in the substantia gelatinosa of the dorsal horn of the spinal cord where enkephalin fibres synapse on the endings of pain fibres carrying pain impulses from the periphery. These synapses, when activated, inhibit substance P release. Enkephalin fibres in the reticular formation activate cells in the same system that then descend to the cord and release enkephalin. Enkephalins and endorphins are found in the amygdala, part of the limbic system, thus adding an emotional element to pain responses.

At a spinal cord level, cells in the dorsal horn 'decide' if pain information reaches the brain or not. T (transmission) cells in the dorsal horn are affected by myelinated (A fibres inhibit transmission) and unmyelinated (C fibres allow transmission) fibres. These fibres are influenced by G (gate or gelatinosa) cells also in the dorsal horn. G cells inhibit passage of pain impulses. G cells are activated by large myelinated fibres and inhibited by C fibres.

*Idiopathic pain disorder*²²⁶⁹

Pain is the main focus of clinical attention and is judged to be psychogenic in terms of onset, severity, exacerbation or maintenance. Value judgements are still alive and well in this area. There are problems of both construct and face validity with terms like 'psychogenic pain'. (Aigner & Bach, 1999) Almost anyone with chronic pain²²⁷⁰ will fulfil the criteria for this disorder. Pain arises from multiple interacting sources: organic²²⁷¹, emotional, cognitive, social, cultural, etc. Pure psychological pain is therefore rare. (Tyrer,

²²⁶⁵ All analgesics inhibit cyclooxygenase (COX), thereby blocking prostaglandin synthesis. COX-1 does 'housekeeping', protecting the stomach lining as well as platelet and kidney function. COX-2 is important in inflammation/pain. Selective COX-2 inhibitors have been implicated in myocardial infarction/CVA. The older agents are non-selective, e.g. ibuprofen.

Equivalent doses of narcotic analgesics (mg): hydromorphone 2.5; oxycodone 5-10; methadone 5; morphine, hydrocodone, and heroin 10; and pethidine 100.

²²⁶⁶ Angina pectoris, broken bone, or wound/burn.

²²⁶⁷ Neuropathic pain: burning/stabbing/pulsating quality; hyperalgesia (increased response to painful stimulus) and dysaesthesia (unpleasant sensation); spontaneous pain; occurring where there is loss of sensation; major deficit e.g. trauma to spinal cord; little response to opiate drugs given on their own.

²²⁶⁸ Injury, surgery (including amputation), or disease.

²²⁶⁹ Also called pain of psychological origin, psychogenic pain, or atypical pain disorder. DSM-IV 'pain disorder' is classified with the somatoform disorders. It was called 'somatoform pain disorder in DSM-III-R and 'psychogenic pain' in DSM-III.

²²⁷⁰ Pain persisting beyond the expected period of healing.

²²⁷¹ Damage to thalamus, internal capsule or cortex may give rise to relatively incomplete anaesthesia, mainly involving distal parts of limbs. Exaggerated response to sensory stimulation and touch may elicit something akin to pain in cases with thalamic lesions. Spontaneous pain is not uncommon. This constellation may mislead the examiner into diagnosing 'hysteria'.

1992) Walsh (2002) advocates a biopsychosocial perspective on pain, a model that accepts multiple inputs²²⁷².

The patient is not pretending; the pain is real to the sufferer. It can affect any body part. The patient usually denies any problem other than pain. There may be secondary alcohol or drug abuse. The pain does not resemble closely known organic patterns such as renal colic or angina pectoris; does not follow known nerve distributions; it lasts for a protracted period of time; contrary to popular belief, it is described in similar terms to organic pain; poor response to analgesics; and a good response to psychotropics, as with antidepressants in 'atypical' facial pain.(Merski & Spear, 1967) However, we should look out for an improbable description of pain; using emotionally-laden words; pain that increases in severity and extent over time; a history of multiple treatments; exaggerated facial expressions; exaggerated abnormal posture; frequent grimacing and sighing; and rubbing of the affected parts. Patients with psychogenic causes for abdominal pain will close their eyes when the examiner palpates 'tender' areas, whereas those with organic causes will keep their eyes open.

Patients having a number of the elements on the '*MADISON Scale*' (Hackett & Bouckomb, 1987) have an increased likelihood of experiencing prolonged and incapacitating pain.²²⁷³

'Psychological pain'²²⁷⁴ is very common in psychiatric patients, especially in neurosis, depression and somatisation disorders. It does not wake the patient from sleep. Operant conditioning may be involved. Those closest to the patient should ideally also be seen by the therapist and the interactions between them and the patient should be observed (are they rewarding him for having pain?). Patients who have been brought up in a household with a chronically ill relative are at risk of 'developing' psychological pain. 'True' physical pain fluctuates in intensity and is highly sensitive to emotions, thoughts, actions, and situational context.

Rather than trying to categorise the patient it is better to identify the various problems each patient has and to deal with them.(Large & Aamir, 2005, p. 99) Treatment strategies advocated for psychogenic pain include antidepressants²²⁷⁵, biofeedback, hypnosis, transcutaneous nerve stimulation (TENS), dorsal column stimulation, surgery (may give temporary relief but is generally ineffective), and psychotherapy (getting a person to examine the emotional ramifications of the pain without saying that the pain is not 'real'). Benzodiazepine and analgesic (including opiate) dependence should be avoided or treated.

Walsh,(2002) a psychologist, lists the main psychological interventions thus: psycho-education, biofeedback, relaxation therapy, stress/anxiety/anger management, supportive psychotherapy, operant conditioning techniques, CBT²²⁷⁶, and outpatient multidisciplinary pain management programmes in specific pain services. Imagework is discussed under cancer.

Patients may sabotage treatment and deny psychological interventions as ineffective. Emphasis should be shifted from passive participation to the patient being active in their own management. Reinforcing of pain behaviour should be identified and discouraged, as should 'doctor shopping'. Non-pain behaviour is praised by therapists and family.

Hysterectomy

Hysterectomy is more likely to lead to depression if there is a prior history of alcoholism or psychiatric illness.(Ballinger, 1977) The risk of depression may have been exaggerated by the inclusion of women with normal uteri who sought hysterectomy for the relief of emotional problems.(Udwadia, 2000) In a prospective study (Ryan ea, 1989) hysterectomy for benign conditions was associated with a high prevalence of pre-operative psychological morbidity (55%), which declined to 31.7% later on. The main risk factors for a poor psychological outcome were the previous scores on mental health measures and personality inventory. Hysterectomy, vaginal or abdominal, for benign conditions led to significantly improved sexual pleasure in a Dutch study.(Roovers ea, 2003) Gutl ea (2002) found less body image

²²⁷² Biological, psychological, emotional, behavioural, social, etc.

²²⁷³ **M**ultiplicity (> 1 site/variety of pain and relief leads to new pain), **a**uthenticity (person spends at least as much effort convincing evaluator of reality of pain as seeking a remedy), **d**enial (denial of emotional difficulties and emotional influences on pain), **i**nterpersonal (presence of significant others worsens pain), **s**ingularity ('my pain is unique because...'), **o**nly the current doctor ('can cure me'...this may not last!), **n**othing helps (constant, non-varying pain – may even get worse).

²²⁷⁴ A.K.A. pain disorder, pain behaviour, or psychogenic/idiopathic/somatoform pain disorder.

²²⁷⁵ TCAs, SSRIs – dual action drugs like venlafaxine or duloxetine may be particularly effective.

²²⁷⁶ Distraction, relaxation, attention diversion, challenging negative pain-related thoughts, etc. Certain cognitions are unhelpful in pain patients, e.g. 'I will always be in pain' (catastrophising) and 'Pain is a message to tell me I am a useless human being' (personalisation).

dissatisfaction after vaginal hysterectomy than after abdominal hysterectomy, the problem with the latter being a visible scar.

Strategies to minimise psychosexual problems after gynaecological surgery²²⁷⁷ (de Marquiegui & Huish, 1999)

Involve partner
 Avoid radiotherapy if possible
 Minimise physical mutilation
 Preserve ovaries
 Reconstruct vagina if possible
 Check sexual activity at follow-up
 Refer for sexual counselling
 Attend to alternative positions, lubrication, intimacy issues, fears and myths, etc

Polycystic ovarian syndrome (PCOS)

Pregnancy or weight gain can precipitate the onset of PCOS. It has also been associated with the use of valproate (in people with epilepsy and/or obesity, so the association with the drug is controversial) and with TLE. Patients on valproate should be monitored for depression, weight gain, type 2 diabetes, metabolic syndrome, sleep apnoea, hirsutism, irregular menses, and acne vulgaris. (Norman ea, 2007)

Mastectomy

One study of survival after mastectomy for breast cancer found that those women who denied their predicament and those who tried to fight harder both did well in comparison to those who gave up trying. Another study found that 25% of women who had this operation had significant psychological symptoms, especially depression, anxiety, and sexual dysfunction. Increased risk for psychological dysfunction is associated with poor marital relationship, unsupportive social network, recent adverse life events, and prior psychiatric disorder. Numerous variables interact to determine psychological health or ill health, e.g. personality, coping styles, immune status, type and stage of cancer, metastatic or non-metastatic disease, marital harmony versus disharmony, surgical and other interventions, and so on. Marital (sexual) problems are sufficiently common after mastectomy to warrant involvement of the husband early on in treatment. The woman may be embarrassed by her disfigurement and feel bad about herself as a person (woman). Prostheses may help. Both partners should be helped to see and touch the scar. Open groups for mastectomy patients have been advocated in the prevention of long-term morbidity. Differences of opinion exist as to whether radiotherapy after mastectomy increases or decreases psychological morbidity. Less radical surgery is used more often today than heretofore. Some women respond worse to loss of their breast than to others. Counselling by a nurse should be given after diagnosis and before operative surgery. Psychiatric morbidity, such as depression, should be recognised and treated. The patient should be given the choice for mastectomy or a less radical procedure since this does seem to reduce the associated psychiatric sequelae.

*Phantom*²²⁷⁸ *breast*

Experience of still possessing the lost breast after mastectomy
 Very common (Jarvis, 1967)

Amenorrhoea:

Secondary amenorrhoea may be of organic or psychological origin.

²²⁷⁷ **Female genital mutilation** (FGM) is most common in Africa but is also found in parts of Asia and among immigrants to western countries. Type I involves clitoridectomy while type 2 also involves removal of the labia minora. Girls may be held down during the procedure. Pain, haemorrhage and infection are common and it is likely that PTSD and other psychiatric disorders are commonplace following FGM. (Burki, 2010) In Guinea, 97% of all females undergo FGM, although some progress is being made to eradicate this practice. Recent figures for Cameroon and Mali were 20% and 92% respectively. (Wakabi, 2007)

²²⁷⁸ Flor (2002) points out that phantom sensations or pain can affect many surgically removed parts, e.g. rectum, penis, teeth, tongue, eye, limb, or breast.

Aetiology

Pre-pubertal
 Pregnancy
 Emotional stress
 Severe organic (e.g. increased prolactin due to chronic kidney disease) or functional psychiatric disorder
 Drugs increasing prolactin levels
 Prolactinoma
 Chronic alcoholism
 Substance abuse
 Pseudocyesis²²⁷⁹
 Excessive physical exercise (e.g. jogging)
 Debilitating illness or malnutrition (including anorexia nervosa)

Hyperemesis gravidarum

This was once considered to be psychogenic and to arise from ambivalence toward the pregnancy. It is no longer viewed in this way. It is one cause of the amnesic syndrome.

Genitourinary medicine (GUM)

The psychological aspects of sexually transmitted infection (STI) have a long history. AIDS phobia finds its early roots in syphilophobia in particular and venereophobia in general. Syphilis accounted for about one in ten psychiatric admissions during the pre-antibiotic era. Non-specific urethritis and herpes were strongly feared in the time gap between the wane of syphilis and the rise of HIV. The shame attached to such conditions was reflected in medical euphemisms such as ‘specific disease’ (syphilis) and ‘gram negative intracellular diplococci’ (gonorrhoea). In 2008 the US Centers for Disease Control (CDC) stated that at least 25% of teenage American girls have an STI²²⁸⁰. (Anonymous, 2008a) Longterm effects of STI include infertility and cancer of the cervix. Numerous important issues are raised by such statistics, such as emotional versus physical readiness for intimacy, condom non-use and needle-sharing, various other risk-taking behaviours, alcohol and substance misuse, and sexual assault. A number of studies demonstrate the high rates of psychiatric morbidity in GUM clinics (Osborn, 2007), much of which goes undetected.

Dialysis

This prolonged procedure, in the case of end-stage renal disease, has been associated with such adverse psychiatric sequelae as depression²²⁸¹, dementia²²⁸², the dialysis disequilibrium syndrome (transient acute confusional state secondary to rapid changes in plasma osmolality²²⁸³), (possibly) encephalopathy due to cytokine activation (reaction to synthetic dialysis membranes), and abnormal marital relationships with much covert anger and lack of healthy communication. The stress of dialysis may lead to behavioural problems in offspring. Aluminium was used to reduce phosphate serum levels, but it was inferior in this regard to calcium carbonate. The pathology of dialysis dementia differed from that of Alzheimer’s disease²²⁸⁴ and the dementia-Parkinsonism complex of Guam. The pathology of dialysis dementia²²⁸⁵ has been described as follows: increased brain aluminium levels; increased number of senile plaques; absence of neurofibrillary tangles; and abnormal tau protein processing with deposition of insoluble phosphorylated tau in grey matter as in Alzheimer’s disease. Wernicke’s encephalopathy has been noted in some cases on longterm haemodialysis who had not received vitamin supplementation. The incidence of suicide is raised among patients on chronic haemodialysis, although not all patients who withdraw from dialysis are suicidal (‘rational suicide’) even if some are also feeling depressed. (Levenson, 2008, p. 1016) It has been suggested

²²⁷⁹ Pseudocyesis is classified under somatoform disorder not otherwise specified in DSM-IV.

²²⁸⁰ The main infections are human papilloma virus, Chlamydia, herpes simples, and trichomonas.

²²⁸¹ This is often untreated. (Watnick ea, 2003)

²²⁸² And osteomalacia: aluminium poisoning – desferoxamine binds iron and aluminium.

²²⁸³ Patients often note progressive impairment as the next dialysis session approaches and may develop brief delirium (minutes-hours) after the session (‘disequilibrium’ because of rapid fluid/electrolyte changes). Such events are much less common with the slower acting continuous ambulatory peritoneal dialysis. However, the potential *full syndrome* consists of nausea, vomiting, headache, myoclonus, hypertension, and (if cerebral oedema occurs) coma and seizures.

²²⁸⁴ As the dialysis patient ages vascular and Alzheimer dementias are more often seen.

²²⁸⁵ Dialysis dementia may still occur where undialysed patients in chronic renal failure receive medication contain aluminium.

that early discussion of the option of dropping out of treatment may reduce later levels of morbidity and mortality. Ideally, a psychiatrist should assess all patients who are being considered for long-term dialysis.

Lithium and the dialysis patient

Lithium is readily dialysed

Patients maintained on dialysis do not excrete lithium

They do not require daily lithium therapy (it is only removed at dialysis)

They are usually maintained on 300-600 mg lithium *after* each dialysis treatment (some people need doses on non-dialysis days)

Serum lithium levels are checked 2-3 hours after a dose (monthly after a dosing schedule is established)

Testosterone levels may fall (often staying within the normal range) in patients with chronic renal disease and cause erectile dysfunction and reduce sperm production.

Restless legs syndrome²²⁸⁶ (RLS)

It has been suggested that RLS emanates from altered dopamine (DA) function in the CNS (reduced threshold in spinal flexor reflex) and/or reduced cerebral iron acquisition (low basal ganglia iron). RLS is equally common in both sexes at all ages (some say it is more common in females: Anonymous, 2003), and it is more common in the elderly. Most sufferers do not seek professional advice, many cases are not diagnosed, and the taking of inappropriate remedies is common.(O'Keeffe ea, 2007) Although most cases are idiopathic/sporadic, there is a positive family history in 92% of people with RLS.(Anonymous, 2003) Families with an autosomal dominant inheritance of RLS with complete penetrance have been reported. Susceptibility to RLS has been linked to specific foci on chromosomes 6p, 9p, 12q and 14q. A variant found on 6p predicted both periodic limb movements of sleep and iron deficiency in RLS patients and in their families.

A Canadian study of familial RLS (Xiong ea, 2010) found a high rate of familial aggregation of RLS (77%), sibling and offspring relative risks of 3.6 and 1.8 respectively, disease duration averaging 24 years, and an average age of onset of 28 years (SD 15); most family members had early-onset of RLS with mild/moderate symptoms.

RLS affects at least 2-5% of the population at some time, and almost 25% of people over 60 years of age. However, according to Medcalf and Bhatia (2006) many cases may start in childhood but are not diagnosed. RLS consists of a very annoying but usually non-painful deep creeping sensation in the calf, less often in the thighs, and rarely in the arms. It mainly comes on when the patient is sitting or lying down for a prolonged time. It causes insomnia but is not confined to bedtime. Social withdrawal and depression may follow. There is an irresistible urge to move the legs. Paraesthetic sensations are usually relieved by vigorous exercise, although relief may be transient in severe cases. It is made worse by sleep deprivation and improved by fever. The sleeping partner may be kicked. RLS may occur for the first time during pregnancy²²⁸⁷ and then remit²²⁸⁸. Myoclonic jerks may be observed during waking hours. Periodic leg movements are usually present during sleep (this combination has been linked in Iceland to chromosome 6p and with decreases in serum ferritin levels of 13% per allele of the at-risk variant: Stefansson ea, 2007).

RLS: other associations

Pregnancy (improves with delivery)

Gastrectomy

Diabetes mellitus

Vascular insufficiency

²²⁸⁶ Although Willis described this condition in 1685 and Wittmaack wrote of *anxietas tibiaram* in 1861 it is more often associated with K. A. Ekbom who wrote about it in 1945.

²²⁸⁷ 19% of pregnant women have RLS, especially in the third trimester; perhaps related to iron deficiency.

²²⁸⁸ RLS usually resolves after delivery.

Excess caffeine
 Antidepressants
 Antihistamines
 Barbiturate or opiate withdrawal
 Uraemia (may herald neuropathy)
 Fibromyalgia
 Amyloidosis
 Acute anterior poliomyelitis
 Myelopathy
 Motor neurone disease
 Peripheral neuropathy (including subclinical sensory) or radiculopathy
 Chronic pulmonary disease
 Hypothyroidism
 Parkinson's disease
 Malignancy
 Malnutrition
 Sleep apnoea
 Iron deficiency²²⁸⁹
 Rheumatoid arthritis (perhaps one-third of cases²²⁹⁰)

Any iron, B12 or folate deficiency should be treated. Reassurance, relaxation exercises, and massaging of affected parts may be sufficient in mild cases. Reducing or stopping caffeine intake may help. Carbamazepine, gabapentin, carbidopa/levodopa (not recommended by Anonymous, 2003), carbergoline (dopamine agonists), pergolide²²⁹¹ (higher doses, as in Parkinson's disease, may be associated with valvular heart disease), pramipexole (Mirapexin)²²⁹², opioids (oxycodone, codeine), clonidine²²⁹³, clonazepam and CBT have been reported to be helpful, and sublingual nitrates may be worth a trial. (e.g. O'Keeffe & Lavan, 1994) However, the hard evidence for efficacy of these drugs varies from limited to poor. (Anonymous, 2003) Rotigotine (Neupro)²²⁹⁴ became available in 2009 for moderate-to-severe idiopathic RLS. 'Augmentation' refers to the phenomenon of earlier onset during the 24-hour day of RLS due to treatment (especially levodopa) and should prompt consideration of a change in medication. Restless legs in association with chronic kidney disease may respond to erythropoietin (for anaemia) or clonazepam and it should disappear after kidney transplantation.

Periodic limb movements of sleep (PLMS)

Every 20 to 40 seconds for periods of minutes or as long as an hour during sleep, perhaps associated with arousals, there are kicking movements, the covers land on the floor, and the patient is often oblivious to these events but may feel tired by day and complain of insomnia. The sleeping partner may be kicked! Most such movements occur during light stage 2 sleep. Background physical disorders are similar to the list for RLS. Age of onset varies enormously. Treatment strategies are as for RLS. Strategies that may be of help include leg stretching, relaxation tapes, and warm baths. PLMS often co-occurs with RLS, and antidepressant drugs may exacerbate both phenomena.

Rheumatoid arthritis (RA)

According to Molodofsky and Chester (1970) poor outcome is associated with low motivation, low IQ, depressed mood not linked to pain, poor impulse control, and poor ego strengths. The specificity of this

²²⁸⁹ Low CSF ferritin (protein storage form of iron) levels have been reported by Early & Connors. (1999) Low CSF ferritin may co-occur with normal serum iron levels. It is important to note that iron is involved in dopamine synthesis and in regulation of the dopamine receptor.

²²⁹⁰ But see Anonymous (2003) who has doubts about a rise in incidence of RLS in rheumatoid arthritis, peripheral neuropathy, and Parkinson's disease.

²²⁹¹ Pergolide (e.g. Periactin), a dopamine agonist, is derived from ergot.

²²⁹² Used for Parkinson's disease. The starting dose for RLS is 0.125 mg, increasing every 4-7 days if needed in steps (0.25 mg, 0.5 mg), the highest recommended dose being 0.75 mg.

²²⁹³ May aggravate depression, or cause insomnia, or lead to a rise in blood pressure if stopped suddenly.

²²⁹⁴ Rotigotine transdermal patches are available as 1mg, 2 mg or 3 mg per 24 hours. Adverse effects include nausea, fatigue, headache and application site reactions.

kind of finding is questionable. Cigarette smoking is a risk factor for RA, especially men who are positive for rheumatoid factor and heavy smokers (Sugiyama ea, 2010). An interaction occurs between cigarette smoking and HLA-DRB1 shared epitope genotype and RA risk. (Karlson ea, 2010)

Fatigue

Fatigue has numerous causes, e.g. excessive work and lack of sleep, worry/anxiety/neurasthenia, depression, lack of stimulation, dissatisfaction, chronic fatigue syndrome, alcohol, benzodiazepines (BZD), beta-blocking drugs, dapsone²²⁹⁵, corticosteroid/alcohol/opiate/opioid/antidepressant drug/BZD/withdrawal, anaemia, dietary deficiencies, myopathies, myasthenic syndromes, MS, motor neurone disease, cardiac/renal/hepatic failure, chronic diarrhoea, chronic pain or infection (including HIV), post-viral, malignancy, connective tissue disease, diabetes mellitus, hypoadrenalism, and hypothyroidism.

Fibromyalgia²²⁹⁶

This is characterised by chronic musculoskeletal (MSK) pain and multiple tender points. These 'points' are commonly found in distressed people are not as specific as was once believed. There is much overlap with anxiety, depression and other 'non-organic' disorders. Poor physical fitness is common.

Fibromyalgia/chronic widespread pain

'Fibrositis' coined by Gowers in 1904

Multiple regional MSK pain, disability

Overlap with symptoms of chronic fatigue syndrome²²⁹⁷ (Sharpe & O'Malley, 2007, p. 156)

Occurs at all ages

Risk factors: older age, female (10 F:1 M), marital problems, alcoholism in family, poverty, self-reported child sexual abuse, injury/assault

Decreased delta wave sleep²²⁹⁸

Abnormal processing of pain²²⁹⁹

Objective signs < subjective severity

Treatment: often unsatisfactory

- Face-saving explanation (sleep loss → pain → sleep loss)
- Graded aerobic exercise improves self-reported health status (Richards & Scott, 2002)
- CBT, coping strategies, relaxation exercises
- Exploration of unresolved problems
- Low dose amitriptyline²³⁰⁰, SSRIs, pregabalin
- Nefazodone (withdrawn) may have therapeutic effects in this disorder

Prognosis generally poor: worse in cases seen in hospitals than in general practice

Osteology, orthopaedics & traumatology

Poor mobility is common in care homes. Predictors of falling in such environments include prior falls, older age, poor balance or functional ability (including dementia), behaviour problems, and psychotropic medication (including TCAs, BZDs, and SSRIs²³⁰¹). (Denning & Milne, 2008, p.360) There is evidence that insomnia as such is a factor in falling. (Avidan ea, 2005)

About 61% of patients operated on for fractured femur develop delirium (Pitt, 1998) and depression, delirium, and dementia increase the chances of dying after hip fracture. (Nightingale ea, 2001) Mental distress in women over 50 years of age may be an independent risk factor for hip fracture, independent of medication effects. (Forsen ea, 1999) Similarly, major depression in women is associated with a reduction

²²⁹⁵ Resulting from methaemoglobinaemia.

²²⁹⁶ See also Henningsen ea.(2007)

²²⁹⁷ The same authors point out that if one doesn't believe that either diagnosis is a medical one they could be replaced by a label of somatoform disorder. In some cases there is hypochondriasis or somatoform pain disorder. (Sharpe & O'Malley, 2007, p. 158)

²²⁹⁸ Deprivation of delta waves in normal people causes fibromyalgia symptoms.

²²⁹⁹ At certain sites there (mainly neck and back) are decreased pain perception threshold (hyperalgesia) and poor pain tolerance; exaggerated skin flare in response to topical capsaicin; dermatographism; allodynia (pain is experienced from stimuli that would not normally be associated with pain; reduced thalamic and caudate blood flow; increase in substance P in CSF; and decreased CSF 5-HT.

²³⁰⁰ Hauser ea (2009) conducted a meta-analysis of antidepressants in fibromyalgia and found that they improve pain and a variety of other complaints. Effect sizes for pain reduction were large for TCAs, medium for MAOIs, and small for SSRIs and SNRIs.

²³⁰¹ Thapa ea (1998) found no difference in falls between TCAs and SSRIs in the elderly.

in trabecular bone, 14% in the femoral bone. (Michelson ea, 1996) Prolactin-raising medication may increase the chances of fracturing a hip. (Howard ea, 2007) Longterm psychiatric inpatients often have low bone mineral density that is related to prolactin levels and chlorpromazine equivalence; they are also often obese and have metabolic dysfunction. (Hallahan ea, 2008)

Avascular/aseptic/ischaemic necrosis (osteonecrosis) of the head of femur leads to severe hip pain. X-rays eventually (weeks) show an area of increased density but are normal initially. Scintigraphy and MRI will show early lesions. Bony collapse may occur. Risk factors include alcohol, corticosteroids, anabolic steroids, heparin, biphosphonates (jaw affected)²³⁰², irradiation, trauma, sickle cell disease, diabetes mellitus, Cushing's disease, HIV, and high barometric pressure (working far underground or deep sea diving [Caisson disease]).

'Athlete's neurosis'²³⁰³ refers to distress in someone who is unable to exercise because of injury or illness and who is heavily emotionally invested in such activity. Back problems have been found to relate to the employer's personality and to job dissatisfaction. Indeed, the best predictor of return to work after back injury is how one liked ones previous employment. (Kirmayer & Looper, 2007, p. 437) CBT may have sustained positive effects on subacute/chronic low-back pain. (Lamb ea, 2010)

12% of patients with Down's syndrome have atlanto-axial instability.

Fractured bones are not diagnostic of child abuse but, in the absence of a confirmed cause should raise suspicion. The site and type of fracture and the child's developmental level may provide clues. (Kemp ea, 2008) Multiple fractures are more common in abuse cases. Rib fractures may also warrant suspicion.

Benign joint hypermobility (joint laxity) syndrome (Bulbena ea, 2004) is probably inherited and consists of multiple hypermobile and painful joints. This disorder of collagen appears to be associated with an excess of anxiety disorders (panic disorder, agoraphobia, and social phobia). These children are often said to have 'growing pains', especially following exertion, and may become unfit as a result of avoidance behaviour.

Marble bone disease (osteopetrosis) is a group of autosomal mild dominant or severe recessive²³⁰⁴ disorders with a very dense, fracture-prone skeleton. Acid phosphatase levels are elevated. Other features in severe cases are intellectual disability and anaemia with early demise. This is one disorder for which stem cell transplantation has been used.

Retroperitoneal fibrosis (chronic periaortitis)

This has many causes, although two-thirds are of unknown aetiology. Smoking, aortic aneurysm, and asbestos are associated with retroperitoneal fibrosis. It may occur with cancer, infection, surgery, or trauma. Drug causes include beta-blockers, methysergide, methyl dopa, ergot alkaloids such as ergotamine and lysergic acid, bromocriptine, cabergoline and other dopamine agonists, and hydralazine.

Toxicity of prescribed treatments

About 0.5% of inpatient deaths are iatrogenic. (Turner & Pearson, 1994) Beta-blockers, isoniazid, lithium, and penicillamine may cause a SLE-like syndrome. Some *anti-cancer drugs* cause encephalopathy and alkaloids are neurotoxic. *Tricyclic antidepressants* may reduce absorption of sublingual nitrates because dry mouth may prevent the tablet dissolving. Especially if given with antineoplastics, *radiotherapy of the CNS* can cause personality change/dementia that may be delayed in onset.

Anticholinergic drugs - side effects (severe in brackets)

Neurological:

- Peripheral: mydriasis, blurring of vision (narrow angle glaucoma), dry mouth (caries), reduced sweating (heat stroke), tachycardia (angina and MI in patients with coronary artery disease), constipation (obstipation/ileus), difficulty urinating (hypotonic bladder & infection)
- Central: difficulty encoding new memory (delirium), restlessness, visual hallucinations, and psychosis
- Physostigmine (**very slowly** 1-2 mg IV) response is diagnostic of atropine psychosis, but normally it is sufficient to stop the offending agent; excess physostigmine may cause a cholinergic crisis (nausea,

²³⁰² This appears to occur mainly in patients with cancer who receive high doses of nitrogenous biphosphonates (e.g. alendronate) given IV.

²³⁰³ Described by Little in 1969.

²³⁰⁴ There is a recessive form with renal tubular acidosis and deficiency of carbonic anhydrase II.

vomiting, bradycardia, and seizures) that responds in turn to an anticholinergic drug such as atropine; carbamazepine has anticholinergic activity.

Jimsonweed (*Datura stramonium*) and related plant species contain the alkaloids atropine and L-hyoscyamine that act as muscarinic antagonists

Drug causes of peripheral neuropathy (not exhaustive: see England & Asbury, 2004):

Sensorimotor neuropathy – vincristine

Sensory neuropathy - metronidazole, flecainide, cisplatin, and large doses of pyridoxine

Mixed neuropathy - nitrofurantoin, isoniazid, lithium, ethambutol, chloroquine, amiodarone, hydralazine, phenytoin²³⁰⁵, and disulfiram²³⁰⁶

Procaine (when given accidentally IV²³⁰⁷)

- May precipitate immediate and short-lived fear of impending demise, hallucinations, or seizures
Management is by reassurance and prevention of self-harm (e.g. restraint)

Beta-blockers (especially propranolol) can cause lassitude, depression, vivid nightmares, & visual hallucinations. *Bromides* are associated with delirium, mania, depression, and psychosis Give sodium chloride IV or orally; if agitated, give antipsychotics (or paraldehyde). *Cardiac glycosides* – in toxic doses these can cause altered visual perception/hallucinations, mania, & delirium. The *clonidine withdrawal syndrome* consists of irritability, psychosis, violence, seizures (withdraw gradually). *Diuretics*, especially bendrofluazide, may cause impotence. *L-DOPA* can lead to mania, depression, schizophreniform, or rapid cycling in bipolars; reduce the dose or stop the drug. Found in OTC diet aids and nasal decongestants, *phenylpropanolamine* can cause psychosis, paranoia, restlessness, anxiety, and headache. In these cases the drug should be stopped.

H2-blockers

Cimetidine (not ranitidine) may cause impotence and reduced sexual drive

Cimetidine inhibits hepatic metabolism of other drugs by competing for pathways:

- Increased anticoagulant effect with warfarin
- Increased sedation with diazepam
- Increased beta-blockade with propranolol

Various *antidotes* may be used for poisons, e.g. ethanol or fomepizole (4-methylpyrazole) for methanol or diethylene or ethylene glycol, naloxone for opioids, flumazenil for BZDs, N-acetylcysteine for paracetamol, atropine for beta-blockers or nerve agents, oxygen for CO, Prussian/Berlin blue for thallium, and dicobalt edetate²³⁰⁸ for cyanide. Antidotes form inert complexes with poisons (e.g. dicobalt edetate with cyanide), speed up detoxification (e.g. N-acetylcysteine), bypass the poison (e.g. oxygen), compete for (e.g. naloxone) or block receptors (e.g. atropine), or decrease the rate of conversion of poisons into even more toxic compounds (e.g. ethanol).

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²³⁰⁵ Rare and only after decades of use.

²³⁰⁶ Usually after months or years of treatment.

²³⁰⁷ Prevention: aspirate needle to ascertain that one is in muscle and not in a vessel.

²³⁰⁸ Alternatives to 300 mg IV dicobalt edetate (repeatable) are IV hydroxocobalmin or IV sodium nitrate plus sodium thiosulphate.

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19

Illicit substance abuse²³⁰⁹

Brian O'Shea

'Because of the strong countertransference reactions such patients evoke, inappropriate diagnostic and treatment decisions may ensue'. (Mack ea, 2003, p. 327)

Direct and indirect costs of substance use disorders to the USA are over \$300 bn annually²³¹⁰. (APA, 2002, p. 255) Annual economic cost of substance use in the UK was estimated as between £10.1 and £17.4 bn. (Godfrey ea, 2002)

The time lapse between the synthesis of a drug and its marketing varies.²³¹¹ Drug-induced psychoses are increasingly seen, especially in young males.

Not all drugs associated with a withdrawal state are dependence producing, e.g. antidepressants.

Dependence may occur with little or no withdrawal. Almost any drug can be abused, e.g. insulin abuse among body builders.

Psychological dependence (habituation) might be mediated by the interaction of a drug with the mesolimbic DA pathway subserving drive-oriented behaviour. Craving becomes strongly cued to environmental triggers.

In the case of physical dependence on opiates, withdrawal (abstinence) symptoms are partly caused by disinhibition of noradrenergic neurones of the locus coeruleus, and of other neurones in the periphery, including gut cholinergic neurones.

²³⁰⁹ Bacchus, deification of ethyl alcohol, cocoa-chewing runners of the Incas and Aztecs, psilocybin-induced states on ancient Easter Island, ache-dulling *Cannabis indica* of Far East sugar cane plantations, 'Purple Hearts' of the 1960s racecourse, amphetamine-induced combat vigilance of twentieth century troops (benzedrine included in US soldiers' kits in WW II), modafinil use by military personnel in Iraq, laudanum abuse by 19th century English poets or more modern use of cocaine powder intravaginally to prolong the 'high' of orgasm, attest to the very human and ancient nature of substance abuse/misuse. Methamphetamine, associated with risky sexual behaviour and more rapid symptomatic progression in AIDS patients, was given as an antidepressant to American women in the 1950-60s. Methamphetamine was first synthesised in Japan in 1919. Clive of India died of an overdose of laudanum at 45 Berkeley Square, London in 1774. (Porter, 1996, p. 107) Nutmeg intoxication (contains myristicine and causes delirium, dry mouth, dizziness, and nausea) has an old pedigree. (Faguet & Rowland, 1978) Synthetic chemicals can be more powerful than the diluted natural alkaloid. *Papaver somniferum* (Oriental Poppy) has been used for centuries for its sedative and analgesic properties. Cocaine was extracted from the coca shrub in 1859. *Psilocybe semilanceata* or Liberty Cap, *Amanita muscaria* (Fly Agaric), and the peyote cactus gave us psilocybin, muscinol, and mescaline respectively. The Assassins of India killed under the influence of *Cannabis sativa*. Substances resembling serotonin with a long history of abuse include psilocybin ('magic mushrooms' – sold openly in Amsterdam, on sale in Irish health shops to January 2006) and substances found in the cohoba bean (*Anadenanthera peregrina*: DMT and bufotenine). Bufotenine (5-OH-DMT or dimethylserotonin) was first isolated from a toad in 1934. In fact, bufotenine is found in a variety of toads, especially *Bufo alvarius*.



Bufo alvarius (Colorado river toad)

²³¹⁰ The National Institute on Drug Abuse (2007: 301-443-1124 or www.drugabuse.gov) put the US societal cost of drug abuse in 2002 at \$180.9 bn, \$107.9 bn of which relate to crime, justice and victim-borne costs. \$15.8 bn went on treatment, research and prevention.

²³¹¹ E.g. 1826 to 1838 for the bromides, 1912 to 1932 for the amphetamines, 1957 to 1960 for chlordiazepoxide, and 1960 to 1962 for diazepam. Time lapsed between first report of drug dependence and common reports of dependence also varies, e.g. 1877 and continuously thereafter for the bromides, 1936 to 1947 for the amphetamines, 1963 to 1966 for chlordiazepoxide, and 1965 to 1966 for diazepam.

The number of substance related deaths in the 27 EU countries and Norway during 2005 lay between 7 and 8 thousand. The greatest increases in such deaths were in Ireland, Greece, Portugal, Finland, and Norway²³¹². (Watson, 2007)

Timeline

1960s USA

Supreme Court held that it was unconstitutional to convict drugs addicts of the crime of having an addiction (*Robinson v California*, 370 US 660 1962) or using substances (*Powell v Texas*, 392 US 514 1968)

During 1960s two types of drug abuser formed the majority of users

Professional - someone e.g. doctor or pharmacist who had ready access to drugs and started taking drugs to relieve psychological or physical symptoms

Iatrogenic - a patient given drugs for pain and became unable to break the habit

Most European countries during early 1990s: about 30% of prison inmates had history of drug abuse; of those inmates who injected drugs 75% were sharing injection equipment

Home Office, England: 5,415 notifications of new narcotic addicts in 1984²³¹³, nearly 30% more than in 1983, and double the number of 1982

Roughly 90% of these new addicts claimed addiction to heroin

About 18% of addicts were seropositive for HIV in 1988, and, in certain areas, such as Edinburgh, the figure was nearer 50%

1984-1992, Ireland: number of heroin abusers stabilised, with rise in the injection of prescribed opiates, especially morphine sulphate (M.S.T.), buprenorphine (Temgesic), and dihydro-codeine tartrate (DF118) **1987, Ireland:** admission rate for 'drug dependence'²³¹⁴ to psychiatric facilities/100,000 population = 6.6

Preventable causes of death in the US in 1990 (% of total deaths)

Tobacco (19)

Diet/exercise (14)

Alcohol (5)

Illicit drug (<1)

National Comorbidity Survey (Kessler ea, 1994): one-year prevalence for (non-alcohol) drug abuse and dependence in the US was 3.6% (5.1% for males and 2.2% for females), while lifetime prevalence was 11.9%

Deaths in both Ireland and Britain, 2000: intramuscular heroin contaminated by *Clostridium novyi* (soil and dust anaerobe; prominent cause of gangrene during the Great War)

Opiate-related deaths in Dublin in 2000 and 2003: 83 and 46 respectively

Dublin: 332 opiate-related deaths (and 253 deaths on its roads) during 1998-2001 (Ryan, 2004)

1999-2001, Britain: number of 14-15 year old who tried cannabis increased from 19% to 29% and 18% to 25% in males and females respectively (Henry ea, 2003)

Face to face interviews of representative sample of people on the Island of Ireland aged 15-64 years

(MORI MRC, late 2002/early 2003 [National Advisory Committee on Drugs & Drug and Alcohol Information Research Unit, 2003]) 70% and 63% response rates in the Republic (ROI) and Northern Ireland (NI) respectively

19% of all Irish ever took an illegal drug (20% NI, 19% ROI)

Most commonly abused drug was cannabis (previous month use: 2.9% NI, 2.6% ROI)

Lifetime prevalence rates for all other illegal drugs were less than 5%²³¹⁵

For lifetime, last year, and last month use of drugs, men outnumbered women (for having ever used cannabis: 23% males, 12% females)

10%, 4%, 1% and 0.5% of persons aged 15-34, 35-44, 45-54, and 55-64 years took illegal drugs in the previous year

6% and 4% of NI and ROI interviewees respectively took ecstasy at sometime during their lives (for cocaine the percentages were 1.7% and 3% respectively)

Cocaine in London in 2004

Smoking freebase cocaine (crack: crystals without the hydrochloride moiety) was twice as common as use of powdered cocaine

Americans aged at least 12 years in 2004

About 19.1 million (7.9%) used illegal drugs during past month

North Eastern Health Board questionnaire study of post-primary schools (Flanagan ea, 2004)

Found the following changes from 1997 to 2002:

Decreased lifetime smoking prevalence - 57.1% to 50.8%

Decrease in regular smoking - 30.7% to 18.2%

No significant change in alcohol consumption - 57.3% drop to 53.7%

Increased weekend binge drinking and feeling drunk more than 10 times - 24% up to 27.2%

Increases in ever (41.2% from 34.9%) and regular (15.1% from 11.9%) illegal drug use

HRB: treated problem drug use in Ireland 2001-6 (Reynolds ea, 2008)

Based on data reported to National Drug Reporting System and to Central Treatment List

Rise in prevalence of treated 'cases' of 15% among 15-64 year-olds (74.8 'cases'/100,000)

168,754 'treatment episodes'

²³¹² The European Monitoring Centre for Drugs and Drug Addiction is based in Lisbon.

²³¹³ Notification ceased to be compulsory in 1997.

²³¹⁴ As distinct from alcohol abuse and alcohol-related psychoses.

²³¹⁵ Ecstasy and magic mushrooms, 4%, amphetamines, cocaine, LSD and poppers [amyl or butyl nitrite], each 3%, solvents, 2%, heroin, 0.4%, and crack, 0.3%.

Increase is mainly due to *same cases* being treated again, i.e. it is a chronic problem
 People on waiting list (longer outside Dublin) not counted, non-reporting occurs, and changes in methodology also reduce figures
 100% increase in new cases in western area

72% of new cases reported polysubstance use

Need for unique case identifier in order to distinguish individuals from treatment 'episodes'

Ireland 1998-2005

According to HRB, among drug users there were 885 non-poisoning deaths (476 due to 'trauma' such as suicide, shooting, and RTAs; 270 due to medical causes such as hepatic or cardiac disease) plus 1,553 deaths directly related to drug use; there were 30 deaths, mostly among teenagers, from volatile substances

Ireland 1998-2007

National Drug-Related Deaths Index: 2,120 drug-related poisoning deaths (55.3% implicated opiates) plus 1,183 non-poisoning deaths (cardiac, respiratory infection, hepatic, etc)

England and Wales 2007 (O'Dowd, 2008)

Big increases in male deaths from opiates (particularly methadone) and cocaine

Ireland 2008-9

Numbers self-reporting ever using cocaine rose from 3% in 2002/3 to 5.3% in 2006/7²³¹⁶

Commonest source of cocaine is friends/family

Reports of 'crack houses' wherein cocaine is turned into free-base rocks

Irish prisons 2003-8: 'over 10,000 prisoners' (almost 4,000 in Clover Hill and over 3,000 in Mountjoy) received methadone treatment programmes²³¹⁷

There are between 13,405 and 15,819 problem opiate users in Ireland and the number of new opiate users entering treatment increased from 809 in 2002 to 1,350 in 2008

Opiate cases, chiefly heroin, presenting for treatment rose from 8,804 in 2002 to 11,538 in 2007 (reasons include service and reporting changes and drug use); fewer cases inject opiates than heretofore; cocaine cases jumping from 954 to 2,643 during the same period

Irish Medical Council (medicalcouncil.ie) stated in 2009 that clinicians must use their registration number on anything that is practice related; they must bear in mind the dependence potential of any drug prescribed; and do not treat opiate dependence unless you are approved under the Methadone Treatment Protocol

World 2009-10

Authors argue that war on drugs is being lost and greatest problems occur where laws are strictest (Wood ea, 2009)

Poorer parts of the world have a greater disease burden per unit of alcohol consumption than do the better off parts of our planet (Rehm ea, 2009)

Driving under influence of illegal substances is now more common than drunk driving in USA, and abuse of prescription drugs is that nation's most rapidly growing drug problem (Anonymous, 2010)

Europe 2010

European Court of Justice rules that minimum cigarette prices imposed by Ireland, Austria and France were contrary to Directive 95/59 but stated that same goal could be achieved by raising tax on cigarettes!

Aetiology

The 'causes' of drug abuse²³¹⁸ and dependence²³¹⁹ are numerous and occur in different combinations and permutations in different individuals.

Genes: Children of alcohol-dependent parents who are reared by non-alcohol dependent adoptive parents have 3-4 times the risk of developing dependence on alcohol than do adopted children whose biological parents were non-alcoholic. In a meta-analysis, Young ea (2004) found the A1⁺ allele of the DRD2 gene to be a marker of substance use and severe substance misuse. A twin study (Agrawal ea, 2004) suggests that part of the association between early cannabis abuse and subsequent abuse of other drugs may be genetic. In particular, genes on chromosomes 1 (e.g. ELTD1), 4 (e.g. GABRA2), and 6 (e.g. CNR1²³²⁰) may increase the tendency to cannabis use disorders (Agrawal ea, 2008) and, in the case of CNR1 variants, of nicotine dependence. (Chen ea, 2008; see Bierut ea, 2008) GABRA2 may be associated with risk for externalising behaviours (including alcohol dependence) but its effect is diminished by parental monitoring of youngsters. (Dick ea, 2009) The C allele of CNR1 may experience greater subjective reward from alcohol. (Hutchison ea, 2008) Various loci may harbour associations with cocaine dependence and cocaine-induced paranoia, e.g. a SNP in the alpha-endomannosidase (MANEA) locus at 6q16.1. (e.g. Farrer ea, 2009) However, environmental influences also seem to be important. Also, using cannabis after discharge

²³¹⁶ See also Abel Thula (2009): during 12 weeks in 2007 9.1% of clients at the Drug Treatment Centre in Dublin had at least one urine positive for cocaine and the majority of these (84.2%) were dependent on cocaine.

²³¹⁷ Of 14 places of detention in the Republic of Ireland, 8 (accommodating 80% of prisoners) offered methadone maintenance in 2009.

²³¹⁸ Substance abuse is a residual category in the DSM system in that it only applies to someone who is not dependent on the drug in question.

²³¹⁹ The main symptom of dependence is the priority given to getting supplies of the drug despite the fact that abstinence syndromes and tolerance are often given great weight in definitions.

²³²⁰ Cholinergic nicotinic receptor 1.

from hospital increases the chances of using other substances.(Aharonovich ea, 2005) Indeed, environment may act to entice a person into substance use whilst genes may influence duration of use.(Kendler ea, 2008) Importantly, most alcohol-dependent individuals do not have an alcohol-dependent first-degree relative.(Kay & Tasman, 2006, p. 414) A genome-wide association study of alcohol dependence found an association with markers rs7590720 and rs1344694 on 2q35.(Treutlein ea, 2009)

Imprinting: It has been suggested that exposure of the mother in labour to drugs might increase the risk for later dependence on drugs in her offspring.

Availability: Dublin held a world record for dipipanone (Diconal, 'Dyke') abuse. Heroin became widely available here since early 1980. Dublin IV drug users have a very high prevalence of hepatitis C²³²¹, and while there was an overall increase in the numbers of heroin users during the period 1991-96 (including increase in female users) there was a relative shift from IV to smoking. Cocaine in socioeconomic (SE) groups 1 and 2 (the 'Celtic Tiger' effect). Proneness to deviancy and neighbourhood drug availability promote marijuana use.(Tarter ea, 2006)

Home: we learn to turn to chemicals at an early age. Excess pocket money, boredom, and lack of supervision.(Robertson ea, 2003) Australian adolescents living with a lone parent were, among other problems, more likely to use cannabis in a study conducted by Rey ea.(2002) Parental knowledge of their children's whereabouts and a confiding child-parent relationship are protective against drug abuse during adolescence (McArdle, 2008) whereas parental smoking increases the likelihood of adolescent substance use and other problem behaviours.(Keyes ea, 2008) Teenage pregnancy correlated with substance abuse in a Swedish study.(Ekéus ea, 2006)

Neighbourhood: Experienced psychiatrists and other health professionals are usually cognisant of potential implications of the patient's address, although it is essential to avoid generalisations. Stahler ea (2009) found that neighbourhood characteristics could have an important influence on treatment continuity and rehospitalisation in dually diagnosed patients, e.g. areas with many vacant houses and higher educational attainment had opposite effects on the follow-up parameters being studied.

Prison: the use of injected drugs and hepatitis C are endemic in Irish prisons; tattooing may be an independent risk factor for hepatitis C in non-injecting prisoners.(Long ea, 2001) Farrell ea,(2002) in a UK national survey of prisoners, found that cannabis, cocaine, and amphetamine use, but not heroin use, were associated with psychosis.

Changes in frontal cortical and subcortical monoaminergic systems during **adolescence** might promote social maturation or confer vulnerability to addictive actions of drugs.(Chambers ea, 2003)

Hero worship: the abuse of drugs by singers or sportsmen.

Peer pressure/need to belong, mood instability of adolescents, and pressure from peer groups²³²² and other pushers. Most young people are introduced to drugs by people known to them rather than by 'pushers'. Knowledge of drug names, but of little else, is common in secondary schools. Many of these children know of others who take illicit drugs and are offered drugs themselves.

Adolescents do not often believe the warnings of doctors and the authorities about the dangers of drug abuse.(Chatlos, 1996) Long-term heavy cannabis users persist with their habit despite acknowledgement of negative effects.(Gruber ea, 2003) Gau ea (2007) found that some factors predicted (male, ADHD, conduct disorder, sibling using tobacco) and others protected against (2 parents at home, good at school, objection to use of substances) substance use in adolescence.

Social status of drug abuse, such as the masculinity of alcohol consumption. Social class is not a protection against drug abuse as such, although certain drugs may be more freely available to different economic groups, such as glues in SE group 5. Macleod ea (2004) found fairly consistent associations between cannabis use and both lower educational attainment and increased reported use of other illegal drugs.

Association of drugs, including alcohol, with holidays, sex, anti-authoritarianism, etc.

Personality disorders, social phobias, and other psychiatric disorders leading to a search for relief in drug taking. Antisocial personality is common in cocaine-dependent persons and childhood conduct disorder is a risk factor for cocaine abuse.(Gamma & Liechti, 2002) Higher cortisol prior to onset of drug use disorder may be a vulnerability factor.(Rao ea, 2009) High impulsivity and low deliberation were found

²³²¹ There were 1,154 and 1,439 reported cases of hepatitis C in Ireland in 2004 and 2005 respectively.

²³²² The fact that the finding that occasional cannabis use predicted later substance use and educational difficulties was influenced by use of tobacco suggested (to Degenhardt ea, 2010) a role for the group to which subjects belonged.

by Love et al (2009) to be associated with increased regional mu-receptor concentrations²³²³ and greater stress-induced endogenous opioid system activation in healthy young male volunteers.

Life crises e.g. combat. Psychoactive substance use disorders significantly co-occurred with borderline and histrionic personality disorders in one study.(Oldham et al, 1995) There is some evidence that patients may use substances as self-medication for PTSD.(Hien et al, 2010)²³²⁴

Introduction to drugs of high abuse potential. Many different chemicals (alcohol, other drugs) and behaviours (e.g. gambling, overeating, and stealing) may have similar effects on so-called brain reward areas, e.g. the ventral tegmental area²³²⁵, locus ceruleus²³²⁶, and nucleus accumbens²³²⁷. Most drugs of abuse that elevate mood cause DA release, e.g. nicotine,(Brody et al, 2004) alcohol and cocaine. Opiates inhibit GABAergic neurones that tonically inhibit DA release. There is some evidence that genetic polymorphism of the D2 receptor is linked to drug abuse, e.g. the Taq1-A polymorphism of the ANKK1 gene (adjacent to the DRD2 gene) and the C957T variant of the DRD2 gene were associated with psychopathic traits in alcohol dependent patients.(Ponce et al, 2008) Substance abuse among patients with schizophrenia does not appear to be influenced by CYP2D6 or CYP2C19 polymorphisms.(Kobylecki et al, 2008) Symptoms of the DTs may be partially related to prefrontal DA hyperactivity. SPECT has revealed chronic dysregulation of the dopaminergic system in detoxified alcoholics. Goldstein and Volkow(2002) describe a I-RISA (impaired response inhibition and salience attribution) syndrome based on a review of neuroimaging studies in drug addicted persons: the orbitofrontal cortex and anterior cingulate gyrus²³²⁸ (regions connected to the limbic system and thought to be important in determining reinforcing stimulus salience) are the usual frontal areas involved in addiction and are activated when an addicted person craves for, binges on, or is intoxicated by substances, only to be deactivated during substance withdrawal. Dom et al (2005) conducted a systematic review of behavioural decision-making and neuroimaging in people with substance use disorders: acute withdrawal was associated with overactivity of orbitofrontal cortex, abstinence with underactivity of this region. Gamma-hydroxybutyrate (GHB, Georgia Home Boy, grievous bodily harm, liquid ecstasy), a GABA derivative, date rape drug (Renner & Ward, 2008, p. 359), and drug of abuse is discussed below.

TV and mass media, e.g. association of alcohol or cigarettes with car racing: media should not glamorise drugs

Classification of abused drugs

- Socially 'acceptable' - tea, coffee, tobacco, alcohol.
- Illicit - perception altering (hallucinogenic, psychedelic, psychomimetic), e.g. cannabis, LSD, mescaline, psilocybin - cause depersonalisation, hallucinations, or mood changes; opium and derived agents - heroin, morphine²³²⁹, codeine²³³⁰ (partially metabolised to morphine), dihydrocodeine, pethidine²³³¹ (meperidine [Demerol] in USA), methadone²³³² (Physeptone to October, 1998, Phymet DTF 1 mg/ml thereafter; Dolophine in US), and so on; sedative-hypnotics - barbiturates, benzodiazepines, etc; speed drugs (psychostimulants) - amphetamines, cocaine, anorectics, anti-diarrhoeals, benzotropine (not available from 2003) and other anticholinergic agents, etc; glues, aerosols, volatile anaesthetics; and others, e.g. pseudo-cannabis.

Classification of drug-induced Psychoses

Serotonergic hallucinogens: LSD, dimethyltryptamine (DMT), mescaline, psilocybin

²³²³ PET study using labelled mu-receptor-selective radiotracer carfentanil.

²³²⁴ Reduction in PTSD severity ameliorated substance abuse but reduction in the latter had only minimal effect on the former.

²³²⁵ The VTA projects dopaminergic fibres to the nucleus accumbens.

²³²⁶ 'Sky-blue place'.

²³²⁷ Rats will readily self-stimulate by lever-pressing to electrically stimulate the medial forebrain bundle (dopaminergic neurotransmission), the latter connecting the ventral tegmental area and nucleus accumbens.

²³²⁸ Szeszko et al (2007), using MRI, found that first episode schizophrenic patients who had used cannabis, had less anterior cingulate grey matter compared with patients who had not used cannabis and healthy controls.

²³²⁹ (5 α ,6 α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol or morphine, after Morpheus (Greek god of dreams) the son of Hypnos (god of sleep).

²³³⁰ (5 α ,6 α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol. Codeine was isolated in 1832 by Pierre-Jean Robiquet. Codeine addiction was a rising problem in Ireland in 2009-10 and is, worryingly, available OTC (without a prescription).

²³³¹ Ethyl-1-methyl-4-phenylpiperidine-4-carboxylate.

²³³² 6-(dimethylamino)-4,4-diphenylheptan-3-one.

Dopamine (DA) agonists: Amphetamine, cocaine, L-DOPA, bromocriptine
Alcohol & Hypnotics: Including withdrawal states
Cannabinoids
Glutamate antagonists: Phencyclidine, ketamine, dextropropion, amantadine
Muscarinic cholinergic antagonists (atropine psychosis): benztropine and related drugs²³³³, tricyclic antidepressants, low-potency antipsychotics, antihistamines
Others: ACTH, corticosteroids, disulfiram, indomethacin, methyl dopa, digoxin, anti-tuberculosis agents, antimalarial drugs, etc.

Abusers themselves can be classified as experimenters, polyabusers²³³⁴, or dependent. It should be remembered the terms 'habit' and 'addict' are not as popular in the official literature as heretofore, having been replaced by the wider concepts of dependence and abuse. Over 20 years ago, the WHO divided drug misuse into hazardous (harm may occur) and harmful (harm has occurred) use. ICD-10 defines the dependence syndrome as 'a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value'. There is a strong desire or compulsion²³³⁵ to take the drug, its use is difficult to control at every stage of its use, and there is a physiological withdrawal state on stopping the drug or reducing its use. There is use of the same or a similar drug to relieve abstinence symptoms and there is evidence of tolerance²³³⁶: the ability of one drug to relieve the withdrawal syndrome of another drug is called cross-dependence, whilst the extension of tolerance from one drug to another is termed cross-tolerance. There is progressive neglect of alternative pleasures and interests, and persistence of drug use despite evidence of harmful consequences.

Signs of drug abuse

The more signs the more likely is there to be a problem
 Many signs also seen in non-abusing normal adolescents
 Qualitative behaviour changes include spending much time alone, irritable if disturbed, excessively unstable mood swings, lying, secretiveness etc
 Poor performance at school (e.g. scholastic failure) or work (e.g. absenteeism)
 Stealing
 Loss/change in interests and friends
 Weight, poor hygiene/health
 Use of drug slang
 Possession of the appropriate gear

Not asking about substance abuse history during admission to psychiatric facilities was common in one London survey.(Barnaby ea, 2003)

*Cannabis*²³³⁷

Cannabis (Gk. hemp) (O'Shea & McCollam, 2001) can mean either a plant (*Cannabis sativa*) or the contained cannabinoids. It is chiefly young cigarette smokers who smoke²³³⁸ it with cigarette²³³⁹ tobacco or

²³³³ *Angel's trumpet* (species *Brugmansia*, family *Solanacea*) is usually taken as a tea made from the trumpet-shaped flowers.(see Hall ea, 1977) It has hallucinogenic and anticholinergic properties and has been used by youth as an LSD substitute. The plant contains parasympatholytic alkaloids such as scopolamine.

²³³⁴ Polytoxicomania.

²³³⁵ Stimulant drug abusers may selectively attend to drug-related words and such bias correlates with increased activation of left prefrontal and right cerebellar cortex on fMRI.(Ersche ea, 2010)

²³³⁶ The need to increase the dose to maintain the original effect as well as the capacity to sustain such dosage increases without endangering life.

²³³⁷ Hashish is also called boom, chronic, gangster, or hemp. Marijuana is also called Marinol, blunt, dope, ganja, grass, herb, joints, Mary Jane, pot, reefer, sinsemilla, skunk (high-THC), or weed. Dagga is grown in South Africa and contains little CBD.

²³³⁸ At least half of cannabis users are also users of tobacco.

chew it (e.g. hashish brownies). Cannabis use in UK youths aged 16-24 years fell from 28% in 1998 to 21% in 2005.

Classification of cannabis based on content and appearance

(Tetrahydrocannabinol [THC] content increasing²³⁴⁰)

'False', e.g. peat, 'grass' (looks like it)

'Grass' (dried, leaves)

'Resin' (dried, compressed blocks)

'Oil'

Also: 'Laced' (mixed with other chemicals, e.g. with PCP in 'superweed')

Cannabis sativa may be grown for

Resin (secreted by flowering tops of female plant: *ganga/hashish*)

Dried leaves (*grass* or *marijuana*²³⁴¹)

Strong, seedless version (*sinsemilla*)

Hemp tea (*bhang*)



Cannabis sativa

'AMP' is marijuana soaked in formaldehyde and then dried. THC, one of many cannabinoids, is the chief active ingredient, with its own receptor in rat and human brain. This receptor is G-protein linked, inhibits neuronal adenylate cyclase, and is found mainly in basal ganglia, hippocampus and cerebellum, with lesser amounts in the cerebral cortex, and is sparsely represented in the brainstem. Anandamide²³⁴² is the endogenous ligand for THC receptors. It is much less potent and has a shorter duration of action than THC. Chronic use has damaged the animal and human hippocampus. (Yücel ea, 2008) Cannabis is home grown or smuggled. It was formerly used in corn plasters.

Possible legitimate uses of cannabis

Appetite stimulation ('munchies') in AIDS

Reduction of intraocular pressure (IOP) in glaucoma (high doses produce transient results - many adverse effects)

To counteract nausea, anorexia, wasting of cancer

MS-related spasticity

Relief from despair of dying

²³³⁹ Cannabis in pipe tobacco was popular in the past. The Netherlands in 2010 represents a paradox: it is legal to smoke cannabis in a cafe but not if it contains tobacco!

²³⁴⁰ The street name for high-THC-content cannabis is '*skunk*'. Cannabidiol or cannabidiol (CBD, C₂₁H₃₀O₂), another cannabinoid, may have antipsychotic properties. (Morgan & Curran, 2008) It has been suggested that the attraction of cannabis for people with severe mental illness relates to relief of dysphoria and anxiety. However, high-THC cannabis, as commonly used today, is low in CBD. (Atakan, 2008)

²³⁴¹ 'Skunk grass' is a hybrid breed with a relatively high THC content.

²³⁴² Sanskrit *ananda*, bliss.

The US Supreme Court found that medical use of cannabis was illegal in June 2005, despite laws in a number of states permitting its use. This does not mean that people in states allowing its use will not get it. (Hopkins, 2005) even though they are not shielded from federal prosecution. (Okie, 2005) A synthetic relative of cannabis, nabilone, can only be prescribed in Britain for nausea due to chemotherapy, and Δ^9 -THC (Dronabinol) is similarly licensed in America. Frank ea (2008) found that dihydrocodeine provided more pain relief than nabilone in patients with chronic neuropathic pain, neither drug being associated with significant adverse events. Dronabinol has modest analgesic effects in multiple sclerosis; side effects include dizziness. (Svendson ea, 2004) According to Cohen (2008), the evidence for effectiveness of cannabinoids²³⁴³ is strong for cancer, central pain, and pain due to spasticity, mixed for acute pain, and poor for peripheral neuropathic pain.

Cannabis causes dependence²³⁴⁴. Mild withdrawal symptoms²³⁴⁵ may follow chronic high-dose (that would be toxic to the novice) intake, indicating some degree of tolerance. These symptoms commence on day one to three after stopping cannabis intake, peak during day two to six, and last from four to 14 days. (Budney ea, 2003, 2004) Tolerance develops to cannabis-induced mood changes, tachycardia, hyperthermia, changes in IOP, and EEG changes.

DSM-IV cannabis abuse and dependence (US survey of > 40,000 adults: Stinson ea, 2006)

Abuse – 12-month and lifetime prevalence = 1.1% and 7.2% respectively

Dependence - 12-month and lifetime prevalence = 0.3% and 1.3% respectively

Associated with abuse/dependence – male, Native American, widowed/separated/divorced, living in West

Not associated with abuse/dependence – Black/Asian/Hispanic

Drug effects depend on the experiences and expectations of the user and co-users, the quality and quantity of the drug, and drug purity²³⁴⁶. Cannabis causes anxiety, panic, dry ('cotton') mouth, a sleepy look, red-eye, over eating, increased confidence, verbosity, and distortions of time, colour and shape. These effects are followed by sleep and, commonly, a hangover. Prolonged use leads causes apathy and self-neglect. A study of monozygotic male twins from the Vietnam Era Twin Registry found that those who had abused cannabis in the past (almost 20 years after regular use) differed from co-twins only on the block design sub-test of the WAIS-R. (Lyons ea, 2004) Heavy users appear 'stoned'. Heavy use of cannabis is associated with poor recall of word lists but this tends to normalise with abstinence. Fear, apprehension, irritability, and a dejected state may also feature. Hallucinations are more likely with high doses of THC.²³⁴⁷ 2.5 mg of THC given IV causes positive psychotic symptoms, anxiety, and impaired neuropsychological performance in healthy adult males. (Morrison ea, 2009) Other problems include bronchitis (and bullous lung disease in young people) and lung, tongue and other cancers²³⁴⁸, aspergillosis, gynaecomastia,²³⁴⁹ priapism, or feminisation (suppression of testosterone). Reports of sudden death among cannabis users may relate to cardiac effects of THC. (Henry ea, 2003) Sidney (2003) argues that death rates from cannabis *per se* are low.

Intravenous crude cannabis extract

- Can cause: nausea, vomiting, abdominal pain, watery diarrhoea, hypotension, pyrexia, arthralgia, acute renal failure, pulmonary oedema, disseminated intravascular necrosis, death

²³⁴³ Side effects include tiredness, sedation, sickness, tingling, and feeling strange.

²³⁴⁴ Dependence is more likely with more frequent use. Withdrawal has been linked to the CB1 receptor and the THC component of cannabis. Prolonged dysphoria after stopping cannabis intake may be due to reduced dopamine activation.

²³⁴⁵ Various combinations of craving, irritability, anger, aggression, restlessness, sweating, tremor, depression, anxiety, insomnia, vivid dreams, tachycardia, nausea, abdominal pain, myalgia, diarrhoea, and anorexia beginning the day after last use, reach maximum intensity on the third day, and wane over the following week.

²³⁴⁶ E.g. lead has been added to marijuana to increase its weight leading to plumbism! (Busse ea, 2008)

²³⁴⁷ THC content in the average marijuana cigarette has increased substantially over the last several decades: from 0.5% in 1990 to about 5% in 2003 in Britain, and, in 'Nederweed', the variety smoked in the Netherlands, there is about 10-11%. (Aston, 2001; Henry ea, 2003)

²³⁴⁸ Cannabis smoke contains 70% more cancer-producing hydrocarbons, e.g. benzopyrene, than tobacco smoke.

²³⁴⁹ Gynaecomastia is also caused by alcohol, cyproterone acetate, digitalis, oestrogens, and spironolactone.

- Admit, manage fluid/electrolyte balance

AMP may cause psychomotor retardation, poor attention, thought disturbance, anxiety, and poverty of speech. Proposed chronic effects include the 'amotivational syndrome' and a schizophreniform psychosis (some experts have interpreted both as representing chronic intoxication).

Controversy exists as to whether early cannabis use leads to depression and schizophrenia. Does it cause or trigger schizophrenia? The evidence is against a simple self-medication hypothesis. (Arseneault ea, 2002; Rey & Tennant, 2002; Zammit ea, 2002)

Cannabis and psychiatric disorder

Cannabis makes schizophrenic delusions and hallucinations worse

Specific cannabis-induced psychosis in clear consciousness - controversial

Toxic confusional state may occur after high doses

New Zealand study (Fergusson ea, 2003) - heavy use in young people independently causes psychotic symptoms

Arendt ea (2007) - depression more likely while taking cannabis than when not using it, and cannabis is taken by depressives for the same reasons as others

Green ea (2005) - 58 studies of varying methodology, 5 of which were epidemiological - found that epidemiological studies consistently reported higher cannabis use and misuse prevalence in people with psychosis

Arseneault ea (2004) - about 8% of schizophrenia could be prevented by eliminating cannabis use

Munich study (Henquet ea, 2005; see also Hall, 2006) - highly suggestive of role for cannabis-related psychotic symptoms, especially in the predisposed

Danish study (Arendt ea, 2005) - cannabis-induced psychosis may be followed, after a gap which may be in excess of a year, by schizophrenia spectrum disorders (see also Arendt ea, 2008)

Carriers of COMT valine158 allele more likely to show psychotic symptoms and develop schizophreniform disorder with cannabis, but 2 copies of the methionine allele protect against this (Caspi ea, 2005)

EEG changes²³⁵⁰ and increased schizotypy have been described in cannabis users (Skosnik ea, 2006)

Panic attacks in panic disorder patients and hypomania/mania in bipolar disorder cases may be triggered by cannabis (Kay & Tasman, 2006, p. 443)

Systematic review suggests cannabis is psychotogenic (Moore ea, 2007)

Evidence for causal relationship with psychosis is not strong (Macleod, 2007) but anything that reduces the burden of schizophrenia is worthwhile; the risk of psychosis if one ever used cannabis is 1.4 that for a person who never used it (Kelly, 2007)

Dutch MRI study of first-episode schizophrenia suggests that brain volume loss is greater over five years if cannabis is used (Rais ea, 2008)

Systematic review (Zammit ea, 2008) suggests that cannabis is associated with increased relapse and non-adherence in psychotic disorders but few studies adjust for baseline illness severity or adjust for potential confounders such as alcohol – adjustments for only a few confounders may greatly reduce results

English fMRI study (Bhattacharyya ea, 2009) suggests that modulation of mediotemporal and ventrostriatal function by Δ^9 -THC may explain effects of cannabis on verbal learning (impaired) and psychotic symptoms (provoked) respectively

Di Forti ea (2009) in London found first episode psychosis patients had smoked stronger cannabis and had smoked for longer and more often than had healthy controls

A systematic review of neuroimaging in cannabis use (Martín-Santos ea, 2010) found that studies differed so much that meta-analysis was impossible; resting global and prefrontal blood flow are lower in cannabis users than in controls; methodological differences lead to different functional findings during cognitive tasks; acute use of cannabis/THC find increased resting activity and activation of frontal and anterior cingulate cortex during cognitive tasks; and the effects of cannabis on brain structure may be small.

Flashbacks, which may result from release of psychoactive components from body fat, are rarely attributable to cannabis as such, but cannabis may precipitate flashbacks due to earlier abuse of powerful

²³⁵⁰ Decreased power and signal-to-noise ratio at stimulation frequency of 20 Hz.

drugs like LSD. Cannabis, like alcohol and cocaine, is associated with reckless (and fatal – Anonymous, 2005) driving²³⁵¹ or flying with effects lasting for up to 48 hours. It increases uterine contractions that can lead to precipitate labour; heavy maternal use may lead to some increased separation of the eyes, tremor, excessive startle response, and decreased visual response to photic stimulation in the newborn. Co-morbid alcohol abuse complicates interpretation. There is a suggestion that exposure to cannabis during the first trimester may be associated with increased risk for childhood neuroblastoma²³⁵².

Cannabis and the law

Illegal in USA, 1937

Medical use legalised in Australia, 1994

Whilst still illegal in Britain, cannabis was downgraded as an offence but upgraded again in 2008 – maximum penalty for possession was increased from 2 to 5 years in prison

Schedule 1 controlled drug under the Irish *Misuse of Drugs Acts*

Irish licence can only be granted for research, forensic analysis, use as an essential ingredient in industrial manufacturing, or (in the case of low THC yield plants) for the growing of hemp

Cannabis use is associated with poor educational, occupational, and interpersonal outcomes, although direction of causality is unclear. (Hall & Degenhardt, 2009) In the author's opinion, there is no realistic hope that associated lawbreaking will disappear automatically if cannabis were legalised. The media should de-glamorise illicit drugs. Medical use of cannabis, preferably by inhaler rather than by smoking, requires more research. The evidence for such use is still weak. (Tobin, 2004)

*Phencyclidine (PCP; angel dust, boat, hog, love boat, **peace pill**)*

PCP (O'Shea, 2000a), an arylcyclohexylamine, relative of pethidine, and former dissociative anaesthetic agent²³⁵³, antagonises glutamate transmission by inhibiting calcium influx at the NMDA receptor. It also activates ventral tegmental DA neurones. It can be smoked (sprinkled on joints of parsley or marijuana), sniffed (snorted), eaten or injected. It can cause dizziness, ataxia, amnesia, excitement, dissociation and a paranoid-hallucinatory state. The pupils of users are small or normal, the skin red and dry. SGOT and CPK levels may be raised. PCP is detectable in urine for up to 8 days. Venlafaxine, O-desmethylvenlafaxine, and dextromethorphan may give false-positive tests for PCP.

Complications

- Hyperpyrexia
- Muscle rigidity
- Dystonia
- Seizures
- Cardiac arrhythmias, tachycardia, hypertension
- Rhabdomyolysis-myoglobinuria-renal failure
- CVA
- Choking (hypersalivation)
- Symptom return after a lapse due to leakage from adipose tissue (flashbacks)
- Failure to form new memories (long term hippocampal potentiation)
- Suicide

Palm test

Hold your palm open and ask patient to name the colours he sees in your palm – LSD patient names various colours and/or images whereas PCP users try to attack your hand. (Abraham & Aldridge, 1993)

Consider PCP intoxication in anyone with nystagmus²³⁵⁴, high blood pressure and an altered mental state. Severe intoxication should be managed in hospital. Anticholinergic antipsychotics may exacerbate

²³⁵¹ An Irish study showed that 9.5% and 15.7% of tested drivers were positive for any drug and cannabinoids respectively. (Bergin, 2007)

²³⁵² *Cancer Causes and Control* 2006;7:663-9.

²³⁵³ Introduced during the 1950s, it was withdrawn because of rat neuronal toxicity and adverse human mental effects. (Johnstone et al, 1959)

²³⁵⁴ Nystagmus may also be found in sedative-hypnotic intoxication or withdrawal. *PCP* (although also causing rotator or horizontal nystagmus) is unique in causing vertical nystagmus.

symptoms of PCP intoxication. Haloperidol may exacerbate the behavioural and cognitive effects of PCP²³⁵⁵, whereas atypical agents reverse them.(Starter & Bruno, 2002) However, antipsychotic drugs are often ineffective and may lower the seizure threshold. Diazepam is often preferred.(Aronow ea, 1980) Avoid acidification of the urine (danger of myoglobinuric²³⁵⁶ renal failure and exacerbation of systemic acidosis) but nasogastric suction with multiple doses of activated charcoal can be employed.

Ketamine (Special K, Ketalar SV, cat Valiums, Kit Kat, vitamin K)

This is a similar drug to PCP (O'Shea, 2000a) and is mainly diverted from legitimate sources such as hospitals and veterinary clinics. It can cause excited behaviour, depersonalisation, hallucinations, delirium, and vivid dreams.

Khat

Catha edulis or the Qat shrub is an Afro-Asian tea plant.(O'Shea, 2000a) Ingestion of the Qat shrub can cause sleep problems, anxiety, depression, anorexia, various GIT symptoms, and, on rare occasions, psychosis.(Cox & Rampes, 2003) The most important ingredients are D-pseudonorepinephrine (cathine) and cathinone. These have central amphetamine-like properties.



Bundle of khat

Complications of khat

- Drug interactions – phenylpropanolamine (in cold cures, appetite suppressants, and prescription drugs – synergism), MAOIs (avoid – sympathetic hyper-stimulation), surgical anaesthetics (may experience bizarre reactions; post-operative agitation/over-arousal)
 - CNS – dizziness, headaches, migraine, ataxia, fine tremor, stereotypy
 - Psychiatric – insomnia; poor concentration; paranoid, schizophreniform, manic psychoses (pure khat-induced psychosis resolves rapidly but may require BZDs and antipsychotic drugs); depression (esp. on cessation of khat use); self-harm/suicide (rare); violence directed against others
 - Cardiovascular – tachycardia, arrhythmias, palpitations, hypertension, vasoconstriction/ischaemia/MI, pulmonary oedema, cerebral haemorrhage, worsening of pre-existing heart disorders
 - Respiratory – bronchitis, tachypnoea, TB
 - GIT/liver - xerostomia, polydipsia, dental caries/periodontal disease, chronic gastritis/gastric ulcer, constipation/paralytic ileus, anorexia, loss of weight, increased risk for upper GIT cancer, cirrhosis
 - GUT/obstetric – impotence, spermatorrhoea, altered libido, urinary retention, reduced birth weight, stillbirth, impaired lactation
 - Metabolic/endocrine – fever, sweating, hyperglycaemia
 - Ophthalmic – conjunctival congestion
- CNS – central nervous system; BZD – benzodiazepine; GIT – gastrointestinal tract; GUT – genitourinary tract; MAOI – monoamine oxidase inhibitor; TB – tuberculosis.

4-methylmethcathinone (2-methylamino-1-p-tolylpropan-1-one, mephedrone, Miaow, MMCA, 4-MCC, Blue Light)

This stimulant, illegal in some countries²³⁵⁷ including Ireland, is bought over the internet and can cause poor concentration, anxiety, depression, euphoria, talkativeness, and paranoid thinking. Users may develop auditory and visual hallucinations and a mania-like state. Rash, tachycardia, arrhythmias, hyperhidrosis, bruxism, trismus, and seizures have been recorded. It may have vasoconstrictor effects. Deaths have been reported.

²³⁵⁵ However, some authors recommend haloperidol for PCP delirium. Chlorpromazine may potentiate anticholinergic effects of PCP and cause severe, prolonged hypotension.

²³⁵⁶ Myoglobin levels are raised in NMS and in patients in restraints or in those taking LSD, PCP, or cocaine.

²³⁵⁷ The UK decided to ban mephedrone and related cathinones in 2010.

4-methoxymethcathinone (para-methoxymethcathinone, methedrone, methoxphedrine)

This stimulant, a substituted cathinone with MDMA- and amphetamine-like effects, can cause mydriasis, sweating, and hyperthermia.

As well as mephedrone and methedrone, the beta keto cathinones sold in head shops (QV) include methylone (3,4-methylenedioxy-N-methylcathinone; Ease; Explosion; MDMC; MDMCAT), butylone (-ketoN-methyl-3,4-benzodioxolybutanamine), ethylone (3,4-methylenedioxy-N-ethylcathinone; MDEC), dimethylcathinone, ethcathinone, 2- and 3- and 4-fluoro-methcathinones (the last of which is also known as flephedrone), and 4-methoxy-methylaminobutyron.

Lysergic acid diethylamide²³⁵⁸ (LSD₂₅, acid, L, blotter, dots, paper mushrooms, boomers, cubes, trips, microdot, yellow sunshines)

Lysergic acid²³⁵⁹ is a constituent of the ergot alkaloids, and LSD is its semisynthetic hydrolytic derivative. (O'Shea & Fagan, 2001) LSD is commonly used as part of the 'rave' scene. (Riley ea, 2001) It is used for its effects on perception and mood. Users may seek help after a 'bad trip', i.e. if frightened, or may be brought for treatment if psychotic. LSD comes in various guises, such as 'microdots' or impregnated blotting paper, stuck to the back of postage stamps, small coloured tablets, in biscuits, in various drinks²³⁶⁰, etc.



Ergot infestation

Psychedelic (Gk, 'to render the psyche visible') drugs as a group appear to act mainly by mimicking serotonin at the 5-HT₂ receptor subtype. As little as 50 micrograms can cause hallucinations. Tolerance to LSD varies widely. Tolerance to its psychosocial effects can occur after a few daily doses (but return after a few days of abstinence), possibly due to desensitisation of 5-HT receptors. The cardiovascular system is much slower to develop tolerance. Cross-tolerance occurs within the LSD-mescaline-psilocybin group, but not between that group and the hallucinogenic amphetamines. Dependence on LSD is psychosocial in origin, with no physical dependence or withdrawal (abstinence) syndrome.

LSD distorts sense of time, colour, sound, movement and distance, increases the amount of REM sleep, and causes synaesthesiae.²³⁶¹

There may be bizarre visual hallucinations of great vividness. Everything becomes very real and familiar. Problems include severe anxiety (bad trip), suicide²³⁶², accidents, homicide, and, probably, the unearthing

²³⁵⁸ In 1943, Albert Hoffman (1906-2008), a chemist working with Sandoz Laboratories, took LSD₂₅ to confirm its reported effects, felt pleasantly sleepy, and then experienced fantastic, vivid images. LSD, the most powerful hallucinogen (syn. psychedelic, psychodysleptic, or less specifically, psychotomimetic) known, was used extensively medically (e.g. abreactive 'psychotherapy' for homosexuality, neuroses, and alcoholism, and induction of 'model psychoses' [attempts to mimic 'functional' psychotic disorders]) and socially (e.g. attempts to find a new 'spiritual dimension' and to 'inspire' musicians) during the 'swinging' 1960s. Some LSD-treated patients are seeking legal compensation and the British NHS agreed to pay stg£195,000 in an out of court settlement to 43 former psychiatric patients who received the drug between 1950-70. (Dyer, 2002)

²³⁵⁹ LSD₂₅ was synthesised by the Swiss chemist Albert Hofmann in 1938.

²³⁶⁰ 'Spike with acid': to surreptitiously put LSD in another's drink.

²³⁶¹ **Synaesthesiae**: stimulation of one sensory modality leading to perception in a different modality, as when sounds are 'seen' or when a light induces voices heard; many people with synaesthetic experiences appear to have normal mental states, as with the man who could feel rounded or peaked shapes when eating different foods or the woman who experienced colours when tasting foods. (see Eagleman, 2010) Synaesthesiae may occur in Parkinson's disease treated with dopaminergic drugs. Cannabis intoxication may include visual hallucinations associated with listening to music.

²³⁶² Especially if psychotic experiences seem 'real'.

of schizophrenic or other psychotic tendencies in vulnerable individuals. Rarely, patients may deliberately damage their own tissues, causing, for example, blindness. Flashbacks of earlier LSD experiences, usually unpleasant and mostly lasting minutes or hours, may occur even years after drug use. They are possibly due to release of stored drug from fat stores, or may be brought on by cannabis use at a later time. There have been some tentative *in vitro* experiments that support a possible teratogenic effect: chromosomal damage has not been confirmed.

LSD in high dosage is suppresses cytokines as well as T, B and natural killer cells.(Spies *et al.*, 2002)

The classical hierarchical approach to psychiatric diagnosis holds that we cannot record the presence of a 'functional' psychosis in the presence of drug abuse. However, the American DSM-IV classification system warns us not to exclude a functional psychosis unless the clinical evidence for a causative role for drugs is compelling. Most clinician will allow time to clarify the most likely culprit.

Treatment of a bad trip may include observation, 'talking the patient down' (reassurance and reality-orientation), and a benzodiazepine, e.g. diazepam 20 mgs orally. Phenothiazines may aggravate the problem if the patient has taken some of the more unusual hallucinogens. If a neuroleptic is required, the choice is between risperidone and haloperidol, the former having been found to block LSD behavioural recognition in rats. Selective serotonin reuptake inhibitors (SSRIs) should be avoided for depression following LSD use as they may lead to recurrent flashbacks²³⁶³.

Ergine (d-lysergic acid amide, LSA)

This LSD-like chemical, an ergoline alkaloid, comes from the seeds of the morning glory²³⁶⁴ plant. These were used by Aztec priests in Mexico for their hallucinogenic properties.

Other hallucinogens

These are less potent than LSD. 'Magic mushrooms' (banned in Ireland from 2006), especially *Psilocybe semilanceata* or Liberty Cap, which contains psilocybin (magic mushroom, purple passion, shrooms), and *Amanita muscaria* (or *muscaria*)²³⁶⁵ or Fly Agaric, containing muscinol, are abused in Ireland and Britain. Mescaline²³⁶⁶ is found in *Teonanacatl*, a Mexican cactus. Mescaline use can lead the user to perceive body parts to be severed or the colour of objects to be altered. MDMA²³⁶⁷ has both stimulant and hallucinogenic properties. Bufotenine, a MAOI, is derived from the skin of pet bufo (and other) toads in the US by licking.(Howard & Foerstl, 1990) It has only one-thousandth the hallucinogenic effect of LSD. Bufotenine can cause sweating, palpitations, vomiting, and faecal incontinence. There are many other examples²³⁶⁸ that can be lethal in overdose - orphenadrine was withdrawn from the market in 1999.



Liberty cap

Post-hallucinogenic perceptual disorder (PHPD)

PHPD is a chronic disorder that can last for years following LSD ingestion.(Smith & Seymour, 1994) The patient reports seeing trails of light or afterimages following hand movements. Patients may experience anxiety or depression. Closing the eyes or going indoors to a darker place may exacerbate PHPD and wearing dark glasses outdoors may help (reduces indoor-outdoor difference in brightness). Some cases have responded to SSRIs, BZDs, or naltrexone.

Gamma-hydroxybutyrate (GHB, liquid ecstasy, liquid X, easy lay, scoop, cherry meth)

This anaesthetic and drug of abuse is derived from GABA and is found in mammalian brain. It is available as a liquid, powder or capsule. . It is sold in sex shops or can be ordered in the post. It is associated with the

²³⁶³ But see post-hallucinogenic perceptual disorder.

²³⁶⁴ Morning glory (*Convolvulaceae*) includes over a thousand species. The best known is *Rivea* (or *Turbina*) *corymbosa*, a perennial climbing vine with white flowers found throughout Latin America.

²³⁶⁵ This and *Amanita pantherina* contain isoxazole agonists of GABA and may induce a drunken state, hallucinosis, disturbed vision, muscular excitability, seizures, and coma.

²³⁶⁶ Buttons, cactus, mesc, peyote.

²³⁶⁷ New Ecstasy, Adam, clarity, ecstasy, Eve, lover's speed, etc.

²³⁶⁸ Such as the behavioural toxicity of anticholinergic drugs.

rave and club scene, date rape, and has putative anabolic effects²³⁶⁹. (Ricaurte & McCann, 2005) Despite its abuse potential, (Caputo & Zoli, 2007) it found a medical use in the treatment of narcolepsy. (Littner ea, 2001) Its euphoriant and disinhibiting effects resemble those of alcohol ('*G-ber daze*'). GHB increases cerebral DA. It is synergistic with alcohol and may depress respiration. Some effects of GHB are reversed by naloxone in animals. (Jones & Volans, 1999. GHB is found naturally in the body, there is a specific receptor for it but it affects many neurotransmitter system (incl. GABA, 5-HT, DA, opioid).

Effects

- Euphoria, sedation, amnesia
- Paradoxical agitation
- Nausea, vomiting
- Muscle stiffness
- Disturbed vision
- Dizziness, confusion, ataxia, abnormal movements
- Respiratory depression/arrest²³⁷⁰, bradycardia, coma and seizures

Body builders may develop physical dependence and withdrawal phenomena, the latter resembling withdrawal from alcohol. BZDs may be needed for severe withdrawal, as may antipsychotic drugs.

Gamma-butyrolactone

This precursor of GHB is converted peripherally to GHB by a lactonase. It is present in some health supplements. It is said to burn off fat, increase sexual potency, and enlarge muscles. Prolonged use may lead to physical dependence and an abstinence syndrome.

1,4-butanediol

An aliphatic alcohol that resembles GHB, 1,4-butanediol is found naturally in trace quantities in the body. It is dehydrogenated to GHB in the body. It is used as a solvent in industry and is found in some health supplements. Toxicity resembles that of GHB but there may be urinary and faecal incontinence. Overdose may lead to abnormal mental state, movement disorder, respiratory depression/arrest, coma, and death.

Opiates and opioids

Some of the research in this area is summarised in the table. Repeated use of opioids suppresses activity of the endogenous opioid system. Opiates and opioids are often 'cut' (adulterated²³⁷¹) with other substances such as cocaine (snowball), strychnine, quinine, lead, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or sodium bicarbonate. Mixtures of mild opiates with anticholinergic drugs (scopolamine, atropine, antihistamines) that increase the sense of euphoria are known as 'T's and Blues' or 'Juice and Beans'. The potential uses of heroin ('scag'²³⁷²) in medicine are detoxification from opiates and opiate maintenance programmes²³⁷³ (van den Brink ea, 2003; Luty, 2005; Rehm ea, 2008; Oviedo-Joekes ea, 2009; Berridge, 2009) and very painful conditions such as bone metastases and laryngeal tuberculosis. In the UK, only doctors with a special licence are allowed to prescribe heroin and cocaine as maintenance treatment for dependent patients. Oviedo-Joekes ea (2009) warn that, because of a risk of overdose or seizures, heroin (injectable diacetylmorphine) should be administered in centres capable of dealing promptly with emergencies. Heroin can be swallowed, injected under the skin or injected straight into a vein²³⁷⁴. It can also be smoked or sniffed²³⁷⁵. Inhalation of heroin can provoke acute severe asthma. 'Chased' heroin involving heating it on tin foil and inhaling the sublimate. Opiates can be detected in urine for 2-3 days.

²³⁶⁹ Used illegally for weight loss, muscle building, and L-tryptophan replacement.

²³⁷⁰ Especially if taken in overdose or with alcohol.

²³⁷¹ Substances added to illicit opioids may cause a variety of complications, e.g. amblyopia, peripheral neuropathy, and melopathy.

²³⁷² Derived from morphine by acetylation of the phenolic and the alcoholic groups on carbon atoms 3 and 6 respectively. Morphine itself was isolated from laudanum in 1805 by Frederick Setürner.

²³⁷³ Not used in Ireland but is available in the UK. A random sample of Irish GPs in July 2009 (Anonymous, 2009) found that 50% opposed the legal availability of diamorphine to heroin addicts while 41% said yes with conditions and only 7% would welcome it. In the same survey, 74% opposed the legalisation of cannabis, 10% had no opinion, and 14% were in favour.

²³⁷⁴ Often dissolved in water with lemon juice to improve solubility. This practice may be associated with Candida blood infection with cutaneous, eye and osteoarthritic consequences.

²³⁷⁵ Intranasal use, according to the Drug Enforcement Administration (DEA) in the US (US Department of Justice, Drug Enforcement Administration, 2003), increased since more pure forms of heroin became available and because users were concerned about the association of HIV and IV drug use.

Capsule of *Papaver somniferum*

The heroin user takes his first 'fix'. An injection leads to intense pleasure, flushing, itching (histamine release), slowed breathing, lowered body temperature, hypotension, and bradycardia, followed by drowsiness giving way to sleep. Anorexia and reduced libido also occur. If he continues to take the drug, he enters the 'honeymoon period' when the drug continues to have pleasurable effects: some users rate it much higher than sexual orgasm. This effect wears away quite soon however, and any attempt to stop the drug is met with withdrawal symptoms.

Opiates & opioids: research findings (abbreviated)

Year	Results	Comments
1974	95% of Vietnam vets gave up opiates on return home	As many as 20% claimed to be addicted ('strung out'); 11% of soldiers tested positive for opiates on being 'demobbed'
1978	36% off drugs, 46% using, 12% RIP	British heroin addict attendees after 7 years
1990	In-patient detox necessary	Too much methadone on Dublin streets
1990	Of notified addicts, 84% addicted to heroin, 6% to cocaine	England
1990	70% of methadone maintenance cases HIV+	Dublin's Pearse St. Mostly young, poorly educated, U/E, * had legal history, injectors, especially heroin
1991	Injecting drug use fastest growing AIDS group	Europe (in Britain, HIV+ injectors still low at < 10%)
1991	Methadone withdrawal more severe than heroin withdrawal!	No difference in onset or duration of symptoms
1992	86% of IV heroin users HIV+	Central Dublin & Dunlaoghaire; 83% were hepatitis B antigen positive
1994	8% of Norwegian population obtained controlled analgesics	Especially older females – dispensed prescription study
1995	Risk of HIV from 1 percutaneous needlestick injury = 1/500	USA
1997	> 40% of Irish AIDS due to IV drug use	69 of 209 cases newly confirmed in 1999 were drug misusers
1998	Male drug users with HIV have more psychiatric problems than other HIV cases	
2000	50-90% of injectors in EU are hepatitis C positive	Females often fund habit via sex industry
2001	130,000 people in US current heroin users in 2000	Aged 12 and over; 0.1% of population
2003	Irish GP's methadone maintenance patients	Many are hepatitis C-positive but a large number were not tested
2005	Irish GP's methadone maintenance patients	22 of 23 hepatitis C positive – knowledge of harm reduction and health implications not associated with reduced high-risk activity
	Pharmacists suspicious of analgesic prescriptions	Welsh study – frequent requests by same person, their demeanour, refusal to consider alternative medications
2004	0.5% of 12th graders used heroin in last month (0.9% in last year)	US Monitoring the Future Study
	Big increase in use of opioid analgesics for non-medical reasons	In US
2005	Outcome 2-3 years after discharge from hospital	5 died; 109 (76%) of remaining 144 interviewed; 54 cases reported recent abuse; 57% on methadone maintenance; 23% abstinent; completion of inpatient course and attendance associated with abstinence; family history of substance abuse negatively associated with abstinence
2007	Methadone maintenance patients (outpatients) – 3	Urine screens used to detect opiates. Less than 24 months in treatment, lower methadone dose, cocaine abuse and intermittent BZD abuse associated with lower

	months in 2004	rates of opiate abstinence; dual diagnosis associated with more opiate abstinence
2008	Dopamine may not be important in opioid addiction	No change in [¹¹ C]-raclopride binding after diamorphine or hydromorphone
2009	Methadone-treated drug users with hepatitis C failed to modify alcohol use	Dublin study
	Deaths related to overuse of methadone, past psychiatric admission, and increasing comorbidity	Scottish study of dispensed liquid methadone.
	Adherence may be measured by doses picked up from pharmacy	Non-adherence associated with supervised consumption, more frequent pick-up, shorter length of treatment, younger age, lower methadone dose, and recent urine positive for opiates
2010	91% relapse to daily opiate use, 59% within 1 week	Dublin study: early relapse associated with younger age, stronger habit, history of injecting, and not entering aftercare; completion of full 6-week inpatient programme associated with significant delay before relapse
	Opiate substitution associated with better survival + reduced chance of cessation in injectors	82% follow-up of 794 Edinburgh primary care attendees who injected drugs

Some clinical effects of opiate abuse

Meiosis (mydriasis in the cases of anoxia due to severe overdose)

Euphoria

Sleepiness²³⁷⁶

Constipation

Amenorrhoea

Self-neglect

Sexually transmitted disease

Infective endocarditis – usually attacks damaged tissue but can attack normal tissue in IV users, e.g. tricuspid valve staphylococcal infection

Hepatitis²³⁷⁷

Abscesses²³⁷⁸

AIDS

Wound botulism in IV users

Anthrax in contaminated heroin

Other infections, e.g. HIV-visceral leishmaniasis co-infection (*L. infantum*) with needle sharing

Necrotising fasciitis

Bruised veins and puncture marks

Thrombophlebitis, venous thrombosis, thromboembolism (pulmonary and systemic)²³⁷⁹

Long sleeves (to cover needle tracks)

Respiratory arrest (large doses - esp. after a period of abstinence is followed by the use of previously tolerated high doses)

As tissue levels fall: agitation, anxiety, and an obsession with the procurement of further supplies

'Heroin pulmonary oedema' - may follow opioid use (can be present despite preserved consciousness; a non-cardiogenic state resulting from increased pulmonary vascular permeability)

Angioedema²³⁸⁰

Oxygen administration can worsen respiratory suppression in those who have taken an overdose of opiates because the latter reduces the sensitivity of the respiratory centre to CO₂. Morphine inhibits the function of

²³⁷⁶ The origin of 'Opium Dreams'.

²³⁷⁷ Hepatitis B virus can cause acute hepatitis or an asymptomatic carrier state in which the hepatitis B surface antigen, HbsAg, can be detected. 954 cases of hepatitis B were reported in Ireland in 2008 (there may be some duplication), 91 more than in 2007.

²³⁷⁸ Flexion at hip + back pain suggests ilio-psoas abscess in injection drug-users.

²³⁷⁹ May be caused by insoluble additives: starch, talc, etc.

²³⁸⁰ Angioedema = episodes of localised, non-pitting swelling of submucosal or subcutaneous tissues. Drug-induced cases may be due to aspirin, NSAIDs, ACE inhibitors, antibiotics, radio-contrast media, or opiates.

natural killer, B, T, and phagocytic cells. Opiates probably have widespread effects on the immune system. (Spies et al, 2002)

Continued use of heroin may possibly lead to an increase in heroin receptors and to tolerance.

Three types of opiate receptor²³⁸¹

μ (mu)
 κ (kappa)
 Δ (delta)

Short-term use reduces noradrenergic neuronal activity in the locus coeruleus - mu (μ) opioid receptors activate the same potassium ion conductance as the alpha-2-adrenoceptors. If heroin is withdrawn there is an 'overcompensation' of normal physiological activity (e.g. small to large pupils and constipation to diarrhoea). This includes excess noradrenaline release. Clonidine reduces noradrenaline release and ameliorates some aspects of the abstinence syndrome. It has little effect on craving.

Opiate abstinence syndrome

Starts 4 - 6 hours after last dose of heroin

May last for over a week

Anxiety, fear, restlessness

Sleep disturbance for days (heroin) to weeks (methadone)

Mydriasis

Rhinorrhoea, lacrimation, sneezing

Aches and pains

'Cold turkey' or 'clucking': excess perspiration with goosefleshing of the skin

Abdominal cramps, diarrhoea, anorexia, loss of weight, dehydration and insomnia

Sudden leg spasms explain the term to 'kick' a habit, i.e. to give up opiate use

Orgasms may occur in either sex during opiate withdrawal (Wise & Gardner, 2002)

Myoclonus resulting from excess production of the metabolite 6-mercaptopurine rarely occurs in very ill patients taking opiates, often with renal impairment. Management includes dose reduction or wider spacing of doses, fluids, and BZDs. Opiate withdrawal is dangerous if the patient has an accompanying significant somatic disorder such as cardiac disease.

Nevirapine, ritonavir, and efavirenz²³⁸² (non-nucleoside reverse transcriptase inhibitors), by inducing P450 enzymes involved in methadone metabolism, can precipitate opiate withdrawal symptoms in subjects taking maintenance methadone. (APA, 2002, p. 201) The oral solution of the protease inhibitor amprenavir contains propylene glycol which is metabolised by aldehyde dehydrogenase; if the latter enzyme is inhibited by disulfiram the patient may develop propylene glycol poisoning. Rifampicin increases methadone elimination and can likewise induce opiate abstinence symptoms.

Pregnant opiate addicts

Often have socially deprived backgrounds, poor antenatal attendance, and frequent hospital admissions

May have hepatitis and HIV infection

Withdrawals (irritability, jitteriness, and, in the absence of infection, hyperthermia) can occur in both the neonate and in breast fed infants (heroin crosses the placenta and is excreted in breast milk)

²³⁸¹ The *mu receptor* is important for analgesia and euphoria. Whilst found widely in the nervous system it is concentrated in dorsal root ganglia of the spinal cord and in ventral striatum.

²³⁸² Efavirenz can give a false-positive cannabinoid test.

Newborn infants of mothers who inhaled heroin²³⁸³ during pregnancy may experience withdrawal convulsions
 Switch mother to oral methadone because it exposes fetus to a regular dose of an opiate that is protein-bound and longer acting
 Women on methadone maintenance who are in receipt of regular prenatal care have superior obstetric outcomes than women whose opiate use remains untreated (Burt & Hendrick, 2003, p. 1519)

Prognostic studies of opiate addicts are summarised in the table.

Opiate/opioid use: prognosis

Year	Results	Comments
1978	¼ to 1/3 abstinent; 10-20% RIP drug-related deaths	7-year follow-up of heroin addicts
1987	Many early relapses; ½ opiate-free after 6 months	50 opiate addicts post-detox in London
1988	71% used opiates within 6 months; 45% abstinent by that stage	British post-detox study
1990	Stopping IV drug abuse may reduce progression from asymptomatic to symptomatic HIV infection	Switzerland
1990	Best outcome if treated in a therapeutic community	12-year follow-up; but only 15-25% voluntarily completed programme
1993	7 of 45 pregnant opiate addicts RIP inside 6 years (AIDS, OD)	Ireland
1994	Deaths in 1980s due to ODs, those in 1990s due to AIDS	UK 10 year follow up of IV users; big change from IV to PO; 78% had been in prison & 41% of these injected in prison
1998	42% of HIV cases were drug abusers	Ireland
2000	16% still using heroin (31% of these injecting)	Cross-sectional survey of methadone maintenance in GP in Dublin; people using & injecting earlier (trend)
2007	HIV commonest cause of death; often unemployed; most misusing substances and in public accommodation	20-year outcome of pregnant opiate users in Dublin

Needle exchange programmes have been initiated in an attempt to reduce the transmission of infectious diseases, particularly AIDS²³⁸⁴. They have been available for less than a decade in Ireland²³⁸⁵. Needle sharing is a highly dangerous and common habit (even in those collecting sterile needles from official outlets) and some injectors may attend only once. Unfortunately, needle exchange has been used by police to target drug users for arrest in some countries.(Csete & Wolfe, 2008) The antidote for an opiate overdose is IV naloxone (Narcan). Other opiate antagonists may induce withdrawal states in established opiate users (e.g. nalorphine). The use of a narcotic antagonist during pregnancy carries the risks of spontaneous abortion, early labour, or stillbirth.(APA, 2002, p. 321)

Topical naloxone (Ghodse, 1986) may dilate the pupil of an opiate user (reversed on methadone withdrawal) but not that of healthy unmedicated subjects. It does not dilate the opposite eye. Naloxone is too short acting and ineffective when given orally. Methohexitone can block naloxone-induced opiate withdrawal symptoms.

Naltrexone²³⁸⁶ (Nalorex)

²³⁸³ Unpredictably absorbed from nasal mucosa.

²³⁸⁴ 60% of American children got AIDS from a drug-using parent.(Editorial, 1995)

²³⁸⁵ The Minister for Justice stated in 2009 that he was not in favour of introducing needle exchange in Irish prisons lest it be viewed as assisting prisoners in criminal activity.

²³⁸⁶ Naltrexone 6-month implant reduces opioid use in dependent, motivated patients.(Kunøe ea, 2009) Similar findings were reported in Hulse ea.(2009)

Orally administered long-acting pure opiate antagonist
 No euphoria or physical dependence, and consistently blocks effects of customary amounts of heroin and other addictive opiates for up to 4 days, depending on the dose of naltrexone used
 May reduce amphetamine use in amphetamine dependent patients (Jayaram-Lindström ea, 2008)
 Side effects: dysphoria, fatigue, headache, anxiety and nausea, vomiting, abdominal pain/discomfort
 Hepatotoxicity – especially in obese patients on high doses (100-300 mg/day); raised liver enzymes (5 or more times normal) mostly normalise when medication is stopped (Anton, 2008)
 Can cause severe withdrawal symptoms if given in full dosage to patient still using or withdrawing from opiates²³⁸⁷
 Naltrexone compresses the withdrawal syndrome into 2-3 days
 If small doses (1-5 mgs. at first) are given every 3-4 hours with clonidine it reduces the duration and severity of withdrawal symptoms compared to clonidine alone
 After a few days, full doses of naltrexone can be given 3 times/week
 Main problem in practice is compliance (APA, 2002, p. 314)
 Main application may lie with opioid-dependent physicians and other health care workers

Ultrarapid heroin detoxification (general anaesthesia for 6-8 hours plus naltrexone) with alleged clearance of the opiate from the body within 2 days (with most abstinence symptoms occurring under anaesthesia) has been carried out but can be dangerous, even fatal.(Strang ea, 1997)

Nalmefene

Novel opioid antagonist that may reduce relapse in alcoholics
 Longer duration of action than naltrexone
 Appears to be safe from a liver standpoint

Clonidine (Catapres), an alpha-2 adrenergic agonist, reduces the autonomic signs of withdrawal from opioids (sweating, chills, gooseflesh, diarrhoea, rhinorrhoea, and eye watering) but not the subjective discomfort. It can also cause systemic hypotension. TCAs inhibit the hypotensive effects of clonidine. Overdose of clonidine can mimic opiate overdose (coma and small pupils). Clonidine exacerbates the central depressant effects of other sedatives, including alcohol. It should never be stopped suddenly.

Clonidine adverse effects

Dry mouth and dry eyes
 Fatigue, sedation, dizziness
 Nausea, constipation
 Hypotension
 Uncommon - insomnia, anxiety and depression
 Rare - vivid dreams, nightmares, and hallucinations
 Fluid retention may occur, necessitating diuretic therapy

Ghodse ea (1994) found clonidine to be of no value as an adjunct to gradual opioid detoxification. Another α -2 adrenergic agonist, lofexidine, a failed anti-hypertensive and structural analogue of clonidine, has been used to ameliorate the withdrawal symptoms from opioids. It does not share clonidine's effects on blood pressure but the blood pressure should be monitored. According to Lingford-Hughes,(2002) lofexidine can be employed in outpatients but clonidine should be used in hospital.

Acetorphan

Inhibits peptidases responsible for enkephalin breakdown

²³⁸⁷ Many practitioners administer a naloxone challenge prior to prescribing naltrexone, e.g. 0.8 mg IM or 0.2 mg IV. Naltrexone-induced withdrawal can usually be ameliorated with alpha-2 adrenergic agonists (clonidine or lofexidine) and, if required, other medications such as benzodiazepines.

Reported to be superior to clonidine for opiate withdrawals
Has to be given (50 mgs) IV twice daily

LAAM (1-alpha acetyl methadol or levomethadyl acetate²³⁸⁸) can be given as infrequently as three times a week instead of daily methadone as an opiate substitute²³⁸⁹. Take-home drugs can then be avoided. It has a relatively low 'narcotic' effect. Higher doses, just as with methadone, may be more effective in reducing craving and blocking euphoria from additional opiate intake. It should be avoided in pregnancy or during breast-feeding. Lingford-Hughes (2002) has expressed concern that LAAM may prolong the QT interval and cause arrhythmias²³⁹⁰. Monitoring of the ECG would therefore appear essential. It has been withdrawn in Europe and received a FDA 'black box' (caution) in the US.

Sublingual buprenorphine (*vide infra*) is also been used as an opiate substitute²³⁹¹ and can potentially be given every second day. Buprenorphine, a partial opioid agonist, slowly dissociates from opioid receptors, which may be used to antagonise the effects of other opioids and to offer a more gradual withdrawal from this class of drugs.(Williams ea, 2002) There are advocates for maintaining opiate addicts on IV heroin (Perneger ea, 1998) but this is controversial (see Farrell & Hall, 1998) and has been viewed as a 'last resort' approach.(van den Brink, 2009) However, Strang ea (2010) in the UK found that supervised injectable heroin led to much less use of illegal heroin than did supervised injectable methadone or optimised oral methadone.

Conflicting results have been reported concerning the value of electro-acupuncture in the management of withdrawal from opioids.(APA, 2002, p. 318)

Methadone²³⁹² maintenance programmes: This practice has been received with a variety of reactions.(Hafford, 2000) For examples, pharmacists may view it as saving lives, substituting one form of addiction for another, or as placing themselves at risk of antisocial behaviour. There is evidence that these reduce illicit opiate abuse (although diversion does occur), reduce criminality and improve social rehabilitation, reduce risky behaviours such as IV drug administration, and help to prevent HIV infection. There is some evidence that methadone may lessen the euphoria induced by illicit opiate use (so-called 'agonal blockade') for as long as 72 hours.(Kreek, 2000) Methadone has a half-life of 15 hours. Whether or not a patient should be kept on daily or twice-daily methadone is a complex issue and is best decided after a thorough knowledge of the individual has been gained. Most patients need 20-60 mgs/day initially. It is safer to underdose at the start, although higher doses (say 60-80 mgs) in the long run may ensure better retention in treatment.(Kamal ea, 2007) Withdrawal symptoms from methadone come on more slowly and last for longer than with heroin. Methadone maintenance in Dublin during the mid-1990s was more likely in people with a long history of drug abuse, with multiple custodial sentences, previous unsuccessful rehabilitation, and positive HIV status. Two-fifths of methadone deaths in Manchester during the period 1985-94 were in people prescribed the drug, and the death rate from methadone increased eight times over those years. Also, while methadone prescribing may reduce other opiate use, it has no effect on cocaine use.(Gottheil ea, 1993) Methadone combined with MAOIs has led to hypertensive crises.

It is important to avoid mixed agonist-antagonist drugs such as pentazocine and butorphanol in this population because they can precipitate abstinence symptoms in opiate-dependent individuals. If a painkiller is required, the patient should be prescribed a short-to-medium-acting opioid, like oxycodone²³⁹³ (Oxycontin) or morphine, and continued on the usual methadone dosage. (If the patient is on buprenorphine rather than methadone one should administer the supplemental opiate *after* the buprenorphine to avoid withdrawal symptoms, switch to methadone, or use other approaches such as NSAIDs, local anaesthesia, or sedation.)

Cocaine lowers the blood concentrations of both buprenorphine and methadone which may have implications for clinical stability.(McCance-Katz ea, 2010)

²³⁸⁸ Derived from methadone in Germany in 1948.

²³⁸⁹ LAAM's very long duration of action makes it unsuitable for an inpatient taper.

²³⁹⁰ Prolonged QTc and *torsade de pointes* led to withdrawal of LAAM in the USA.

²³⁹¹ There is considerable experience of using buprenorphine during pregnancy – neonatal signs are less marked than those associated with methadone. Its effectiveness in pregnancy has been shown by Fischer ea.(2006)

²³⁹² Whilst methadone binds to mu receptors it also acts as an NMDA receptor antagonist. It can be given once daily for managing opioid addiction but needs to be given every 6 to 8 hours for pain relief.

²³⁹³ Oxycodone is abused by people looking for a high or buzz (Carise ea, 2007) and is replacing heroin in the US as a starting point for opiate abuse.(Renner & Ward, 2008, p. 359)

Patients on stable methadone maintenance should not be automatically excluded from being considered for organ transplantation.²³⁹⁴ Neither should they be pushed into coming off methadone before transplantation. (DiMartini et al, 2007, p. 296)

Methadone poisoning: Methadone²³⁹⁵ contributes to half of opioid overdose-related deaths in England and Wales and to 20% in Australia - heroin is the biggest killer in this regard in developed countries, commonly in combination with alcohol and BZDs. A non-tolerant individual may die after taking 40-60 mgs of methadone.

Indicators of methadone toxicity

Stupor, coma
Small pupils
Shallow breathing
Bradycardia, hypotension
Hypothermia, cold and clammy skin
Apnoea, cardiac arrest, terminal (hypoxic) mydriasis

Treatment includes airway maintenance, gastric lavage, IV fluids, and IV naloxone (0.4-2 mgs every 2-3 minutes) if required. If there is no response after a total of 10 mgs naloxone the diagnosis should be reconsidered. Respiratory depression may return after the action of naloxone wanes, so continued monitoring is mandatory. Methadone is a rare cause of choreiform movements. (Wasserman & Yahr, 1980)

Methadone and QTc prolongation

May occur with higher doses or if there is structural heart disease e.g. as left ventricular dysfunction or other risk factors (low potassium level, cytochrome P450 inhibitors²³⁹⁶, TCAs, etc)

ECG monitoring indicated in such higher risk cases (Krantz & Mehler, 2006; Hussey et al, 2009)

Methadone should be avoided if a patient has a prolonged QT interval

Changing to buprenorphine²³⁹⁷ may be an option in serious cases

Opiates and sex

Sexual behaviour tends to decline in people on long-term regular opiates

This probably has more to do with reduced sexual arousal than with erectile problems

Some people develop erections with naltrexone (due to reduced tonic opioid-mediated inhibition of spinal reflexes?)

Reduced sexual desire, reduced penile erectile ability, and anorgasmia are common in chronic opiate users

Opiates and constipation (see Becker & Blum, 2009)

Methylnaltrexone bromide (Relistor), a peripherally-acting mu-opioid receptor antagonist relieves opioid-induced constipation with interfering with (central) pain relief; it is indicated for use in patients with advanced disease where laxatives have failed; it may cause abdominal pain and flatulence

Alvimopan, another peripherally-acting mu-opioid receptor antagonist, should only be used with inpatients because of an increased risk of myocardial infarction

The laxative danthron (Codalax, Allax) causes liver and intestinal tumours in rodents; human use should be confined to terminal cases

Alpha-Methylfentanyl (China White)

This synthetic analogue of the dissociation analgesic fentanyl dates to 1980. It has been responsible for many deaths from respiratory depression²³⁹⁸. The features of its abuse are those of opiates in general.

Buprenorphine (GGs)

²³⁹⁴ Lifestyle *per se* should not be a block to beneficial medical interventions because then could not only remove smokers and other substance users from consideration but also rugby players and mine workers.

²³⁹⁵ Often taken with other drugs in overdose.

²³⁹⁶ Methadone clearance is decreased by CYP3A4 inhibitors, e.g. cimetidine,azole antifungals, macrolide antibiotics, and some anti-HIV drugs.

²³⁹⁷ Various ways of doing this have been described but the methadone needs to be tapered first and mild withdrawal symptoms should be evident before giving buprenorphine.

²³⁹⁸ Fentanyl-laced heroin and cocaine (Flatline, Drop Dead, Lethal Injection) can be lethal. (Boddiger, 2006)

Buprenorphine (Temgesic), a synthetic opioid, is a *partial* agonist of μ opioid receptors that has been used as a heroin substitute²³⁹⁹, although controversy exists as to whether it is as effective as methadone for maintenance²⁴⁰⁰. (Krantz & Mehler, 2006; Anonymous, 2007; Schottenfeld et al, 2008) It is taken sublingually or by IM or slow IV injection for pain. It is often used postoperatively (epidural), when it has been reported to cause a psychotic state with hallucinosis. Addicts may break down the tablets and inject then IV. Side effects include drowsiness, nausea, vomiting, dizziness and sweating. It may rarely cause respiratory depression. Naloxone only partially reverses its effects. Buprenorphine has also been used as an opiate substitute because it is associated with less physical dependence and toxicity than methadone. A buprenorphine-naloxone combination tablet (Suboxone), developed in the US, became available in Ireland in 2007: when the tablet is placed under the tongue only the buprenorphine is absorbed, but both compounds are absorbed if the combination is injected. It is used in willing addicts aged 15 years and older. Buprenorphine abuse is no stranger to Ireland. (O'Connor, 1988) Ho et al (2009) warn that prescribed buprenorphine may be diverted for recreational use, may cause medical complications, and may rarely cause death if taken in overdose with other sedatives. They state that its low misuse potential is based on animal studies and that its partial agonist role may be exaggerated, that IV use of buprenorphine can cause euphoria and opioid-like effects, and that its potential for illegal use is similar to that for morphine. Sublingual preparations are 'often injected' and use of the drug can give rise to abstinence effects because of its 'higher affinity than methadone for opiate receptors'. IV buprenorphine can lead to skin infection, infective endocarditis, and risk of contracting HIV or infectious hepatitis. (Ho et al, 2009)

Sedative-hypnotics other than benzodiazepines

Examples of sedatives are ethyl alcohol, methylated spirits, methaqualone hydrochloride²⁴⁰¹, diphenhydramine hydrochloride (and other antihistamines), chlormethiazole edisylate (clomethiazole: Heminevrin), paraldehyde (remember that the major site of metabolism is the liver, only a small amount being excreted via the lungs), chloral betaine (Tricloryl syrup²⁴⁰²), and the barbiturates. While all of these are associated with occasional abuse, only meprobamate and the barbiturates will be considered further.

Meprobamate: Marketed first in the 1950s, meprobamate is a derivative of the muscle relaxant mephatesin. It acts by potentiating adenosine²⁴⁰³. Restrictions on benzodiazepine prescribing in New York State led to an increase in prescriptions for the more toxic meprobamate! In overdose it formed a lump or bezoar in the stomach, which, if not extracted by gastroscopy, could break up and cause a second relapse into a comatose state.

Barbiturates (Barbs, Goof Balls): Barbiturates are metabolised by the hepatic microsomal enzyme (P450) system and metabolites are mainly excreted through the kidneys. Barbiturates increase GABA activity on the GABA-A (GABA_A) receptor complex. The medical uses of these drugs are dwindling: prophylaxis in convulsive states, general anaesthesia, and, possibly, abreaction. Their use as a hypnotic in narcosis or a sedative in very disruptive patients is now very rare. They cause both psychological and physical addiction. The actress Marilyn Monroe died from barbiturate overdose.

- **Clinical effects**

- Disinhibition, psychomotor slowing, confusion
- Incoordination, slurred speech
- Nystagmus, mydriasis
- Coma

- **Stages**

- Few hours after last dose – dependent user tense, anxious and tremulous
- Later - muscle twitches, weakness, dizziness, dyspepsia, vomiting, insomnia, alertness, and even convulsions
- (Aggression released in some users)
- Long term - may alter vitamin D metabolism causing osteomalacia with hypocalcaemia

²³⁹⁹ Buprenorphine displaces most opiates from receptors and, in dependent cases, can precipitate a withdrawal state if opiates are currently in the body. It is therefore important to withhold this drug until at least mild abstinence symptoms occur.

²⁴⁰⁰ Buprenorphine is as effective as methadone in detoxification from opioids but it may not cover high doses of opioids because its effects plateau as the dose increases. (Anonymous, 2007)

²⁴⁰¹ Combined with an antihistamine in the now defunct preparation Mandrax; also called Quaalude, Sopor, Parest, ludes, quad, and quay.

²⁴⁰² 500 mgs./5 mls., 1G. nocte max. or 500 mls. b.i.d. to t.i.d. for daytime sedation.

²⁴⁰³ Adenosine is sedative and caffeine antagonises adenosine.

Tolerance is due to a number of factors, such as liver enzyme induction and neuronal adaptation. Cross-tolerance to other sedatives, such as alcohol and BZDs, may occur. Withdrawal from barbiturates should be conducted in hospital whenever possible. It takes about 10-14 days to carry it out safely. Various drugs have been used for this purpose, including barbiturates (e.g. short-acting such as pentobarbital for inpatients and longer-acting such as phenobarbitone for outpatients: 30 mgs of phenobarbitone per 100 mgs of short-acting agent), long acting BZDs, and chlormethiazole. Phenytoin, an anticonvulsant, is ineffective in preventing seizures secondary to barbiturate withdrawal. If a patient has become dependent on opiates²⁴⁰⁴ and barbiturates or other sedative-hypnotic agents should be kept on the opiate until withdrawn from the sedative-hypnotic. Older people on barbiturates for many years (a rarity today) should not be forced to undergo heroic detoxification if their dependence is not causing problems.

Drugs associated with a delirium tremens-like withdrawal state

Alcohol
Barbiturates
BZDs
Glues
Methaqualone

Barbiturates, but not BZDs, increase the metabolism of TCAs. Short-acting and long-acting barbiturates can be detected in urine for 1 day and 3 weeks respectively.

Cocaine (Coke, snow, blow, bump, C, candy, Charlie, coke, etc)

1.2 million Americans were current cocaine users in 2002 (0.5% of population), and 265,000 were crack users. Estimated cocaine use over the previous 12 months in Europe and 15-64-year-olds rose from 3.5 million in 2004 to 4.5 million in 2005. According to Farren (2008) 1% of the Irish population used cocaine during the last month and lifetime use increased from 2.9% to 5% in the period 2003-7.



Erythroxylon coca

Cocaine blocks DA uptake. Cocaine (O'Shea & Stokes, 2000) is derived from the shrub *Erythroxylon coca*. It has been used as a local anaesthetic. It can be smoked, sniffed, or injected.

Crack²⁴⁰⁵ is a pure form of cocaine that is smoked for rapid effect. Crack users may develop tolerance to large doses. Crack causes a sudden rise in blood pressure. Cocaethylene is a toxic metabolite of cocaine that is produced in the presence of alcohol; simultaneous users of alcohol and cocaine²⁴⁰⁶ report enhanced euphoria; as well as cardiotoxicity, there may also be a propensity to violence.

Cocaine inhibits the dopamine transporter²⁴⁰⁷. There is a rise in DA levels in the nucleus accumbens. There is evidence for loss of vesicular monoamine transporter protein (VMAT2 – distinct from synaptic DA transporter) in human cocaine users, a possible indicator of damage to striatal DA fibres.(Little ea, 2003) Chronic haloperidol use leads to upregulation of postsynaptic DA receptors which can reduce the amount of cocaine needed to cause euphoria.(Marder & Wirshing, 2003, p. 484) Clozapine may increase cocaine levels in plasma.(Farren, 2008) Apart from inhibition of the DA transporter, conditioned cueing²⁴⁰⁸, cocaine-induced priming (reintroduction of a drug in formerly dependent user with subsequent increased

²⁴⁰⁴ These include buprenorphine and methadone.

²⁴⁰⁵ Cocaine separated from HCl base (therefore 'free-base'), melted, then smoked (pipe, cigarette). Sold as 'rocks' or as a 'line'.

²⁴⁰⁶ The combination appears to be increasingly employed in Ireland.(Lyne ea, 2010)

²⁴⁰⁷ Transporters for noradrenaline and 5-HT are inhibited to a lesser degree.

²⁴⁰⁸ This activates various brain areas and involves various neurotransmitters.

drug intake – can be blocked by micro-injection of DA antagonists into medial prefrontal cortex), stress (modulated by noradrenaline and extra-hypothalamic CRF – lofexidine and CRF antagonists modulate noradrenergic and CRF responses to stress²⁴⁰⁹), and frontal cortical inhibition (an effect of drugs on the frontal lobe – blamed for compulsive behaviour associated with drug-taking and ameliorated by modafinil) are among neurobiological mechanisms proposed for cocaine addiction.

Cocaine

- Strong psychological dependence – typically the patient binges for 2-3 days, followed by a slightly longer break during which he/she ‘crashes’ – financial resources and drug availability determine level of cocaine use
- Peak effects of smoked or IV cocaine reached in 3-5 minutes
- Peak effects of snorted cocaine reached within 15-20 minutes
- User feels very well, is in great spirits, feels powerful, is socially gregarious
- May have ideas or delusions of persecution²⁴¹⁰
- May hallucinate - may experience subcutaneous sensation called ‘formication’²⁴¹¹ or ‘cocaine bug’ (amphetamines can also induce this)
- Sparkling peripheral ‘snow lights’
- Insomnia, impaired thinking, and panic
- Dental neglect (local anaesthesia masks pain)
- Pneumothorax²⁴¹², gastric ulcers, weight loss
- Cerebrovascular accident
- Myocardial (or other organ, e.g. spleen: Devitt ea, 2005; McLaughlin ea, 2009) infarction²⁴¹³
- Nasal septum perforation, chronic sinusitis, subperiosteal abscess, pneumomediastinum, pneumothorax, pulmonary oedema - in snorters
- Ulceration of the vagina (local use)
- HIV (needle sharing²⁴¹⁴)
- Road traffic accidents
- Seizures
- Hyperthermia
- Feminisation in chronic users
- Smoking cocaine can exacerbate asthma or COPD and lead to a form of pulmonary fibrosis called ‘crack lung’ (Tashkin, 2001)
- Chorea, choreoathetosis, dystonia, akathisia, eye blinking, and lip smacking (‘crack dancing’)
- Cocaine overdose – mostly metabolised in < 1 hour – intubate and give O₂ if needed; monitor ECG; if agitated or delirious or convulsing give BZDs (antipsychotics may cause potentially fatal hyperpyrexia); urine acidification is not recommended for cocaine intoxication; do not give beta-blockers for hypertension (**danger of paradoxical hypotension and worsening of cocaine-induced coronary spasm**) – phentolamine (2-5 mg IV) may be used; chest pain responds to aspirin, nitrates or BZDs

These effects may be transient or persistent. Similar effects have been attributed to amphetamines and nor-pseudoephedrine. Low doses of cocaine may cause toxicity in the presence of congenital pseudocholinesterase deficiency.

Body packers (‘mules’)

Ingest drugs like cocaine or heroin packed in condoms or wrapped in cling film

Enquire as to what is in the packs

X-ray abdomen to show location and number of packs

Carefully remove *gastric packs* with gastroscope or use a laxative (e.g. lactulose) to help passage (**avoid** paraffin-based preparations as they may corrode packs)

For *intestinal packs* employ laxatives or whole bowel irrigation

For *rectal/vaginal packs* employ manual removal

Observe in hospital until all packs removed

²⁴⁰⁹ Cocaine-dependent individuals exhibited higher stress and craving for CRH compared with controls in one study. (Brady ea, 2009)

²⁴¹⁰ E.g. drug dealers or police looking for him or people want to steal his cocaine.

²⁴¹¹ *L. formica*, a bug.

²⁴¹² Due to employing a Valsalva manoeuvre to aid drug absorption.

²⁴¹³ Increased creatine kinase levels in the absence of MI may occur in cocaine users; measurement of serum troponin I (cardiac marker unaffected by cocaine) may be a useful indicator of MI. (Weber ea, 2000)

²⁴¹⁴ The first case of HIV from needlestick injury in Ireland was in 1995.

Rupture of packs can cause psychosis, fever, or rapid death

Body stuffers

Ingest drugs to evade detection/arrest

Swallowed substance may be free or packaging may be poor

While physical dependence on cocaine occurs, abstinence symptoms are often mild. In treatment, the drug should be stopped abruptly and the patient should not be able to procure supplies of cocaine. The worst of the withdrawal symptoms are over within a week. The patient should be monitored for depression and suicidal tendencies. Propranolol (avoid if taking cocaine – *vide supra*) and amantadine may have some ameliorative effects on cocaine abstinence symptoms.

Cessation of intake in chronic, heavy cocaine users may lead to

Fatigue

Nightmares

Insomnia/hypersomnia

Excessive appetite

Psychomotor retardation or agitation

Suicidal ideation²⁴¹⁵

Symptoms peak in a few days

Cocaine use during pregnancy²⁴¹⁶

Prematurity

Poor fetal growth

Microcephaly

Vasospastic fetal CVA

Neonatal cocaine withdrawals

Poor sleep/feeding

Irritability

Seizures

Abnormal EEG and brainstem auditory evoked responses with slow return to normal

Managing cocaine craving²⁴¹⁷

TCAs – poor/transient reduction in craving

Fluoxetine - 40 mgs – some reduction (Lingford-Hughes, 2002)

Disulfiram²⁴¹⁸ - may improve abstinence rates (Carroll ea, 2000)²⁴¹⁹

Baclofen (GABA-B receptor agonist), tiagabine (GABAergic), and modafinil - reported to reduce cocaine craving

N-acetylcysteine²⁴²⁰ (LaRowe ea, 2007)

Vigabatrin may have efficacy (Brodie ea, 2009)

CBT - may reduce cocaine use (Carroll ea, 2004)

Cocaine vaccine undergoing trials²⁴²¹

²⁴¹⁵ Acute brief depression and a lower intensity persistent dysphoria (lasting a few months) have been described and may be due to depletion of dopamine.

²⁴¹⁶ The specificity of such findings to cocaine has been challenged by Frank ea (2001).

²⁴¹⁷ Nearly all cocaine addicts experience intense craving for the drug, especially for the crack form. Farren (2008) believes that pharmacological approaches add little but is more positive about the benefits of CBT, interpersonal psychotherapy, regular group therapy, telephone-based continuing care, and contingency management (basically, rewards for staying off the drug).

²⁴¹⁸ Blocks aldehyde dehydrogenase and dopamine β-hydroxylase. This leads to a rise in plasma dopamine (DA). If cocaine is ingested the rise in DA is much greater, with resultant dysphoria.

²⁴¹⁹ Although it may (Lingford-Hughes, 2002) or may not (Carroll ea, 2004) work by reducing alcohol intake.

²⁴²⁰ A cysteine prodrug which increases glutamate exchange activity.

PET shows areas of poor cerebral perfusion in chronic users. PET also found a decrease in D2 and D3 receptor binding in cocaine-dependent individuals and such cases may also have lower levels of endogenous dopamine than is found in normals. (Martinez et al, 2009) Urine and serum toxicology may be negative for cocaine because of its very short half-life (detectable in urine for 6-8 hours), but metabolites, especially benzoylecgonine, can be detected for over one week. Homicide may occur as a result of cocaine abuse.

*Amphetamines*²⁴²² (*Amphetamine, Speed, Dixies, Bennies, truck drivers, LA turnaround, etc*) Amphetamines abuse is very common, (DrugScope, 2000) especially among young people. It directly releases DA (reversed transport) and blocks noradrenaline uptake, effects potentiated by TCAs. Amphetamine sulphate (can cause coagulation problems, hyperthermia, and renal failure) can be snorted. Amphetamines are used to treat ADHD, narcolepsy, and, in America, unresponsive depression. A questionnaire study of amphetamine prescribing in the English Midlands (Moselhy et al, 2002) revealed that they are being prescribed by a few drug services as a substitute for illicit use. Those with relatives who have Tourette disorder are at risk of developing tic disorder if given stimulants. The FDA declared a total ban on sales of dietary supplements containing ephedra in 2004. This herb (*Ephedra sinica*²⁴²³) contains amphetamine, was popular as an aid to weight loss, and was associated with 155 deaths and many adverse effects, including psychosis and mania²⁴²⁴. The classic members of the group are dextroamphetamine and methamphetamine²⁴²⁵ (*crystal, tea, ice, Tina, crank, etc*). Methylphenidate²⁴²⁶, ephedrine and propranolamine are related drugs²⁴²⁷. Propranolamine and ephedrine can cause hypertension, psychosis and death. Seizures may follow amphetamine use. Amphetamine psychosis²⁴²⁸ usually, but not always, ceases on stopping intake of the drug: the patient is over-responsive, and is less thought disordered or hallucinated than is the patient with schizophrenia. Phenothiazines may increase dysphoria and agitation in amphetamine users; 'talking down' and, if needed, benzodiazepines may be used. Hypertension is treated with benzodiazepines or, if severe, phentolamine. Beta- and combined alpha- and beta- blockers should be avoided²⁴²⁹. Secondary mania has been attributed to amphetamine. Longterm high-dose amphetamine use may lead to stereotyped behaviour e.g. inability to stop tidying. Amphetamines decrease resistance to bacteria, viruses and tumours. Cell-mediated immunity in particular is decreased. (Spies et al, 2002) Combining amphetamine or other sympathomimetic drug with an SSRI, especially if the dose of SSRI is increased, could potentially cause a transient psychosis. Urinary acidification may increase amphetamine clearance. 'Ice' (pure amphetamine) can be smoked in a pipe or on aluminium foil or taken IV.

'Designer drugs'

Cheap and synthetic

Can resemble the usual drugs of abuse

²⁴²¹ The carrier is cholera toxin B subunit. This is linked to a nor-cocaine derivative at methyl ester group as immunogen. The hope is to reduce the effects of cocaine and to prevent relapse. Patients may only respond if they achieve at least 43 mcg/ml IgG anti-cocaine antibody levels. (Martell et al, 2009)

²⁴²² Amphetamine was developed by Alles in 1927. (O'Shea, 2000b)

²⁴²³ It was called *Mormon's tea* when used as a drink.

²⁴²⁴ Hypertension and cardiac arrhythmias were reported. When combined with another stimulant (e.g. caffeine) it may be lethal. It does cause weight loss. It can still be acquired via the internet!

²⁴²⁵ **Methamphetamine** (methylamphetamine, N-methylamphetamine, desoxyephedrine, originally synthesised from ephedrine by the chemist Nagayoshi Naga in 1894, has a long duration of action and its euphoric effects can last up to a day. It can be taken PO, PR, snorted, smoked (*crystal*), or injected. It was called *Fliegerschokolade* when given to German pilots. Prolonged use causes mental dulling. Intracerebral haemorrhage and, when inhaled, non-cardiac pulmonary oedema has been reported.

²⁴²⁶ Ritalin, JIF, MPH, R-ball, Skippy, the smart drug, spit tobacco, vitamin R. Stimulants, including methylphenidate, may have an association with sudden unexplained death in youths. (Gould et al, 2009)

²⁴²⁷ The UK Medicines and Healthcare Products Regulatory Agency announced in 2007 that methamphetamine precursors pseudoephedrine and ephedrine (used in flu remedies) may become prescription only drugs. (Gunter, 2007)

²⁴²⁸ This was described by Connell in 1958. The psychosis tends to subside over about a week, but cases persisting for months are not unknown.

²⁴²⁹ Potential exacerbation of stimulant-induced cardiovascular toxicity.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP - contaminant in heroin), causes Parkinsonian syndrome.

New drugs appearing all the time, e.g. PCP derivatives, alpha-pyrrolidinophenones, and phenethylamines
Piperazines include 1-benzylpiperazine or BZP²⁴³⁰ (herbal ecstasy²⁴³¹), 1-(3,4-methylenedioxybenzyl) piperazine or MDBP, 1-(3-chlorophenyl) piperazine or mCPP (already employed as a probe in research), 1-(4-methoxyphenyl) piperazine or MeOPP, and 1-(3-trifluoromethylphenyl) piperazine or TFMPP; amphetamine-like 'party pill' drugs sold in various mixtures; can be toxic, including serotonin syndrome

Crystal: This form of methamphetamine is used as a replacement for cocaine or mixed with heroin. The euphoric effects are reported to last longer than those of cocaine do. A number of laboratories have been discovered in Indiana. Use is associated with increased libido and unsafe sex. Concerns have been raised about its role in the spread of HIV among homosexual men in the US.(Boddiger, 2005) Exposure to high doses of methamphetamine causes longterm changes in neurotransmitter systems.(Nordahl ea, 2005) It is sold as a powder for injection, inhaling²⁴³², or oral consumption.

Dopamine sensitisation (reverse tolerance) with psychostimulant exposure

Repeated use of methamphetamine may lead to schizophrenia-like psychosis

Previously non-psychotogenic adverse events may precipitate psychosis if methamphetamine was taken in the past

With repeated use of methamphetamine there is increasing dopamine release

Philip Seeman²⁴³³ suggested multiple pathways to dopamine supersensitivity: social, physical, and environmental

Dimethoxybromoamphetamine (DOB, snowballs): A warning was disseminated about this synthetic agent in 2003 by the National Advisory Committee on Drugs²⁴³⁴ and the Gardai. This powerful hallucinogen is often mistaken for ecstasy and, because of a delayed effect (3 hours), impatient users may take more than one of these white tablets. Big doses can result in amnesia. Vascular spasm may lead to gangrene. Agitation is common. Depending on dose, effects last for 8-24 hours. Benzodiazepines such as diazepam or lorazepam may be used for hallucinations. Vascular spasm may require heparin and/or intravenous or intra-arterial nitroprusside.

Naltrexone may reduce amphetamine use in dependent subjects (Jayaram-Lindström ea, 2008) and methylphenidate may decrease the tendency to inject amphetamines IV.(Tiihonen ea, 2007)

3,4-methylenedioxymetamphetamine²⁴³⁵ (MDMA, ecstasy, X, XTC, E, Adam, Clarity, Lover's Speed, Red & Black, White Dove, White Burger)

This phenylisopropylamine is a synthetic oral amphetamine.(O'Shea, 2000b) E blocks 5-HT uptake by the neurone, inhibits serotonin breakdown, and induces its release by the neurone. Regular use leads to

²⁴³⁰ BZP was sold in so-called 'head shops' as a 'natural high' and can have many toxic effects: itch, vomiting, insomnia, hyperventilation, anxiety, agitation, psychosis, chest pain, tachycardia, palpitations, hypertension, hyperthermia, tremor, dystonia, dizziness, headache, confusion, collapse, seizures, urinary retention, and renal toxicity.(see McNamara, 2009)

'Head shops' (McNamara ea, 2010) and the **Internet** became part of a new drug market. Head shops tend to describe/disguise products as bath salts or plant foods and to mark them as 'Not for human consumption'! Illegal laboratories change the chemistry of illicit drugs in order to pass them off as legal substances. A little ammonium will convert coke to crack! Gamma-butyrolactone (GBL), a euphoriant, was banned in the UK in late 2009. *Salvia divinorum*, a hallucinogenic plant containing salvinorin A, was available through head shops.(Pillay & Kelly, 2010) As of May 2010, a majority of head shops closed down precipitously in the Republic of Ireland following the passage of an Order placing 'legal highs' under the *Misuse of Drugs Act 1977*, e.g. selling certain of these drugs could now attract a life sentence! Further legislation appears necessary to stem this menace.

²⁴³¹ Also A2, Frenzy, and Nemesis: the reader should not assume too much from these names, e.g. herbal ecstasy may also refer to ephedrine.

²⁴³² Crystals are heated and the vapour is then inhaled.

²⁴³³ Professor of pharmacology at University of Toronto, born Canada 1934, discovered dopamine D2 receptor in 1974.

²⁴³⁴ Est. July 2000 to improve knowledge and understanding of drugs of abuse.

²⁴³⁵ It was synthesised in the 1960s but never marketed. According to Lacy and Sworowski (2002) it was considered as a potential chemical warfare agent by the US Army during the 1950s and it was employed as a self-awareness/empathy-enhancing agent by psychotherapists during the 1970s. It was neurotoxic in animals.(Renner & Ward, 2008, p. 359)

tolerance (and increased intake). MDMA street samples are often impure²⁴³⁶ and may contain no MDMA at all!

Effects

- Intense empathy (5-HT flooding) that decreases with chronic use
- Paranoid psychosis, flashbacks, anxiety, restlessness, agitation, irritability, panic, depression, confusion
- Fatigue with insomnia
- Anorexia, nausea
- Mydriasis
- Sweating, fast pulse rate
- Lockjaw, teeth-gnashing, myalgia, stiffness
- Asthma
- Seizures, collapse, hypotension, pyrexia
- Thrombosis, stroke
- Disseminated intravascular coagulation, rhabdomyolysis, acute renal failure
- Ventricular arrhythmias
- Accidents
- Serotonergic neuronal damage²⁴³⁷

Immediate verbal memory is affected rather than visual memory – effects may last a few weeks or for much longer periods with lifetime abuse, (Bhattachary & Powell, 2001; Schilt et al, 2008) although it has proved difficult to exclude the effects of premorbid functioning, IQ, personality variables and the effects of ethanol. (Lacy & Sworowski, 2002) Excess fluid intake may lead to increased ADH levels in the presence of E, and reduced renal competence: the patient may collapse, develop metabolic acidosis, and become water intoxicated and hyponatraemic. There are several related compounds. (O’Shea, 2000b) Withdrawal from E can be associated with anxiety, tremor, dysphoria, fatigue, lethargy, nightmares, headache, sweating, myalgia, stomach cramps, and increased appetite, all lasting for up to a week and peaking after a few days. Sildenafil may be added to E (*sextasy*). Severe E intoxication is managed with IV fluids plus dantrolene. E users should drink small amounts of fruit or isotonic drinks rather than water. Other causes of hyperthermia must be considered, such as infection, heat stroke, NMS, serotonin syndrome, malignant hyperthermia, anticholinergic drugs, salicylate poisoning, amphetamines, cocaine, etc. SSRIs inhibit E uptake and block the euphoriant effects. Deaths associated with E in England were typically associated with taking other drugs as well, especially opiates, although 7% of one series of E-associated fatalities were due to E alone. (Schifano et al, 2003)

3,4-methylenedioxyamphetamine (MDA, *old Ecstasy*) is a close analogue of MDMA. It destroys 5-HT terminals in experimental animals. A related agent is 3,4-methylenedioxyethylamphetamine (MDE, *Eve*).
*Ephedrine*²⁴³⁸

Ephedrine-containing products are sold at some parties as herbal ephedrine.

Effects

- Persecutory ideas, delusions, auditory and visual hallucinations, insomnia, anxiety, agitation
- Tremor
- Palpitations,
- CVA, seizures
- Hepatitis
- Death
- Positive drug screen for amphetamine

²⁴³⁶ Methamphetamine, theophylline, and caffeine among others may be present.

²⁴³⁷ SPECT and PET data suggested that lower 5-HT transporter density/binding in recent users might return to normal over time. (Buchert et al, 2004; Selvaraj et al, 2009) However, ecstasy might have a specific toxic effect on thalamic 5-HT neurones. (de Win et al, 2008)

²⁴³⁸ Amphetamines (analogues of ephedrine) were produced as a replacement for naturally occurring ephedrine in asthma treatment. (O’Shea, 2000b) The ancient Chinese knew ephedrine.

*Glues, aerosols, volatile anaesthetics*²⁴³⁹ (*laughing gas*²⁴⁴⁰, *poppers, snappers, whippets, etc*)

The usual user is a young boy or teenager. Most cases are occasional experimenters and a small minority is involved in solitary abuse. Regular abuse leads to psychological dependence. Young people in care and from social class V are over represented among deaths from inhalants. Over 4% of all deaths among boys aged 10-14 years in the UK during the early 1990s were due to solvent abuse. Of 75 deaths in the UK in 1996 one-fifth were female. There is little difference between the sexes in rates of abuse but males are more likely to die from it. The commonest agents involved in glue sniffing are solvents and adhesives and range from petrol to deodorant sprays. These often contain very toxic compounds (e.g. benzene, naphtha, nitrites, toluene, acetone, carbon tetrachloride, and aliphatic acetates). Petroleum distillates may lead to aspiration. Corrosion may complicate sodium hypochlorite (bleaches), denture cleaning tablets, etc. Nail polish and nail polish remover contain acetone and have caused coma in overdose! Inhalation of petrol is a problem in some developing countries because of its lead content. Computer cleaning materials may be applied to mucosal surfaces using a nozzle, so-called 'dusting'. Abusers inhale (jag) in order to become intoxicated (smashed or stoned). The glue may be warmed before it is inhaled from a plastic bag or milk bottle held over the face.

Physical withdrawals are rare. Following intoxication there may be headache, abdominal aching, cough and red eyes that may persist for a few days. However, abrupt cessation can sometimes be associated with an alcohol-like abstinence syndrome. Tolerance may develop with prolonged use. Early effects are similar to those of alcohol.

Mechanisms of sudden death in solvent abusers

Anoxia - inhaled vomit

Suffocation - plastic bag over head

Vagal inhibition - reflex from laryngeal stimulation because of direct spraying of aerosols – can also cause cold burns and laryngospasm

Respiratory depression - direct result of general depression of CNS

Cardiac arrhythmias – possibly sensitisation of myocardium to adrenaline and sympathetic stimulation – 'sudden sniffing death syndrome'

Trauma - accidents

Explosions/fires – unsafe storage of large amounts of inflammable solvents

Suicide

Delusion that one is able to fly - nearly one-quarter of solvent inhalers in one study (Evans & Raistrick, 1987)

Fluorinated hydrocarbons in aerosol propellants can cause spasm of the larynx. Cardiac arrhythmias are more likely to occur in glue sniffers if they exercise, become hypoxic or hypokalaemia, or possibly if halothane is given. Peripheral neuropathy is associated with the hexacarbons. 'Glue sniffer's rash' is a facial rash caused by repeated inhalation from a bag. Amyl and butyl nitrites are sometimes inhaled for their vasodilator properties in homosexual encounters.

Evidence for permanent structural brain damage with associated psychiatric manifestations is controversial.

Amyl nitrite ('poppers')

Smooth muscle relaxant used for angina pectoris

Glass ampoule crushed in a handkerchief and vapour is inhaled

Rumoured to increase sexual performance and orgasm – nitrites cause penile engorgement and relaxation of the sphincter ani

Can cause transient headache, tachycardia, hypotension, and dizziness

High doses can lead to nausea, vomiting, syncope, cardiac arrhythmias, glaucoma, coughing, wheezing, and dyspnoea

²⁴³⁹ If we omit drunk driving, inhalants are potentially the most lethal form of substance abuse.

²⁴⁴⁰ *Laughing gas* (nitrous oxide, 'shoot the breeze') is obtained from medical sources or from whipped cream dispensing machines ('whippets').

Chronic use may lead to tolerance, dermatitis/burns (perioral/nasal) and methaemoglobinaemia (treated with oxygen and, if needed, 1% methylene blue)
 Activated charcoal reduces absorption from the gut²⁴⁴¹.

The clinical picture may be divided into acute and chronic.

Solvents

Acute effects

Excitement, euphoria, giddiness, disorientation, ataxia, strange behaviour, visual hallucinations, photophobia, powder about the face, and blurred vision

Chronic effects

Mental - fatigue, depression, agitation, poor concentration

Neurological - tremor, cerebral oedema, and cerebellar degeneration

Haematological - bone marrow depression, anaemia, leucocytosis, haematuria, and hypotension

Respiratory - stomatitis, rhinitis, bronchitis, pulmonary congestion, halitosis and anorexia

Cardiac - dilated cardiomyopathy

The abuse of 'over the counter' drugs, such as cough bottles, has been a major problem in some areas.

Toluene

Present in commonly used adhesives

Causes acute dizziness, euphoria, and perhaps hallucinations, convulsions and impaired consciousness (toluene encephalopathy), and longterm paranoid psychosis, intellectual dysfunction and temporal lobe epilepsy

Diffuse atrophy in cerebrum and cerebellum with white matter hyperintensities

Fetal solvent syndrome (Costa ea, 2002) – due to exposure to high dose toluene in utero – resembles fetal alcohol syndrome

Interventions that have been employed, with some good effect, include family and individual psychotherapy. The efficacy of publicity campaigns remains controversial. Solvent abuse is not illegal. Most abusers give up the habit eventually; some continue through to adulthood, and a few go on to abuse alcohol and other drugs. Inhalant-induced psychosis has been treated with carbamazepine (low EPS potential and does not lower seizure threshold).(Mack ea, 2003, p. 351)

Management of substance abuse

Motivation to come off drugs, including alcohol, is often a fleeting and changeable phenomenon. The patient should not be alienated, but should be encouraged to discuss his reasons for taking drugs.

Discussion and advice may be all that is required in the case of those experimenters who occasionally dabble in drugs for reasons of group hedonism. Deeper levels of dependence may require detoxification and assessment and treatment of psychiatric and physical (e.g. hepatitis) problems. Supervised urine sampling²⁴⁴² may be done for a few days, on a daily basis, to test for drug use and motivation before entering treatment. Alternatively, it is used on a regular or random basis to test for compliance. Recently passed urine should be warm. Direct supervision is essential.

Examples of detoxification regimens include reducing doses of lorazepam, chlordiazepoxide, alprazolam, or diazepam for alcohol dependence, and methadone syrup in reducing doses over about 7 days or more for opioid dependence.

²⁴⁴¹ The use of multiple-dose activated charcoal in the treatment of poisoning is being debated.(Eyer & Eyer, 2008; Eddleston ea, 2008)

²⁴⁴² E.g. amphetamines and cannabis are detectable for up to 2 days and (in chronic users) 4 weeks in urine respectively.

At present the main treatment agency for Ireland is based at the Drug Treatment Centre, Trinity Court, 30-31 Pearse Street, Dublin 1. Psychiatric hospitals may also treat these patients but it is advisable to treat them away from other patients. Strict security is required. Health Boards²⁴⁴³, especially the Eastern Region, expanded the number of clinics for drug abusing patients so that there were 4,556 people receiving methadone and 417 on a waiting list in the latter region in 2000 (8,029 people received methadone in Ireland in 2008). Coolemine Therapeutic Community (in north Dublin near Blanchardstown) offers a drug-free rehabilitation programme. The Garda Drug Squad is available for advice and guidance at Harcourt Square, Harcourt Street, Dublin 2.

Services for so-called dual diagnosis²⁴⁴⁴ patients require systematic co-ordination. There are at least three models of service provision in Ireland: parallel, integrated, and serial. (MacGabhann *et al.*, 2004)

Prognosis

Drug abusers in general do better if they come from a higher socioeconomic group, if they do not have an antisocial personality disorder or a family history of alcoholism, and if they have little in the way of physical or psychiatric problems.

Prognostic factors (Dunne, 1993)

Good

Non-opiate abuse, older age when starting, single drug use, more time in therapy, and fewer treatment arrests

Poor

Opioid abuse, low educational level, poor school attendance, and antisocial behaviour

Abuse of drugs by psychiatric patients is common and may exacerbate psychosis, increase non-compliance and hospitalisation rates, increase treatment resistance, and lead to violence, suicide, homelessness, criminality, family discord, and rejection by mental health services.

Prevention

Correct attitudes towards drugs at home are essential. Education plays some role on an individual level but whether it has a broader effect is more controversial. The HSE spent over six hundred thousand euro on an anti-recreational cocaine campaign in 2008 and found that 73% of under-35s stated that poster ads changed their thinking about cocaine and 93% said that radio ads offered novel information on the toxicity of alcohol-cocaine mixing. (Gantly, 2009) Prevention of smuggling, illegal manufacture and international trading by customs and police officials, including Interpol, is an on-going process. Three times as much is spent in the UK on enforcement and supply reduction as on prevention and treatment. Adequate police powers under drug misuse legislation are necessary. A 'Drug Tsar' was appointed in the UK in the late 1990s to co-ordinate anti-drug activities. Self-monitoring by the professions is crucial. General social measures such as employment and housing programmes are very important.

A drug abuser *per se* cannot be admitted as an involuntary patient under the Mental Health Act 1983 in England but the Irish 1945 Mental Health Act allowed for such admission. The (Irish) Mental Health Act 2001 is the same as the 1983 legislation in this regard. Both acts allow for involuntary admission of the same patient if his mental state warrants it. New mental health legislation in the Republic of Ireland brings Irish law into line with British legislation in this regard. The Dutch have taken a relatively liberal approach to drug dependence. This has received a mixed international reception. More than half of US federal prison inmates in 1994 were there for drug offences, many of which were non-violent. Arguments continue that drugs are only a problem because they are illegal. However, this approach ignores the damage done by alcohol and tobacco that are legal.

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²⁴⁴³ Now subsumed under Health Services Executive (HSE).

²⁴⁴⁴ Here meaning substance abuse and an Axis I diagnosis (some authors use the term to cover combined Axes I and II). *Triple diagnosis* means Axis I, substance abuse and HIV/AIDS.

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20

Abuse of 'legal' drugs

Brian O'Shea

'Thou hast the keys of Paradise, oh just, subtle, and mighty opium!' Thomas De Quincey (1785-1859), 1822.

Steroids

It can be difficult to distinguish between steroid-induced psychiatric disorder²⁴⁴⁵ and psychiatric disorder secondary to the disorder being treated. Steroids are more often causative when used in high dosage. Depression is more common than mania, which in turn is more common than mixed affective states. Other associated disorders include schizophrenia-like and delirious states. Reduction in steroid dosage, neuroleptics, lithium, or ECT may be required.²⁴⁴⁶ Anecdotally, TCAs may exacerbate the problem. (Hall et al, 1978) Patients with affective disorders take longer to recover than do those with delirium. Over 90% of patients with steroid-induced psychiatric disorder are recovered within 6 weeks of onset. There is a case for baseline psychiatric evaluation before starting high dose steroid therapy. Some patients develop psychological dependence on corticosteroids and they may strongly resist their discontinuance. They cause increased body weight (increased appetite, fluid retention, and redistribution of fatty tissues). Reversal of these changes, together with corticosteroid-induced skin atrophy, may make the patient look old and wrinkled. Many users of anabolic steroids 'stack' i.e. use various combinations of such drugs in order to achieve maximum effect.

Benign intracranial hypertension (BIH)

Reported with withdrawal from high steroid dosage

Especially in children

Irritability, headache, vomiting, papilloedema, poor sight and sixth cranial nerve palsy

CSF under increased pressure but otherwise normal

May cause permanent CNS damage

Management: increase dose, then withdraw very slowly

Cerebral vasculitis

Confusional state without localising signs

Occurs during withdrawal from prolonged steroid treatment

Management: as for BIH

²⁴⁴⁵ Testosterone levels may be reduced in anabolic steroid abusers. Prolonged depression of HPA axis contributes to sterility and depression.

²⁴⁴⁶ If the patient is steroid dependent it may be necessary to increase steroid dosage before each ECT treatment.

In the early 1990s 6.5% and 1.9% of American adolescent boys and girls reported non-prescription use of anabolic steroids (roids, juice). 1-5% of high-school European and American students admitted to using anabolic steroids in a study conducted by Thiblin and Petersson.(2005) Both physical and psychological dependence have been described in weight lifters using anabolic androgenic steroids (oral or IM) to increase athleticism or enhance physical appearance. Anabolic steroid abuse (see Rashid ea, 2007; Sjöqvist ea, 2008) is, however, not confined to athletes. A narcissistic body image is common among users of anabolic steroids, as is personality disorder (antisocial, paranoid, histrionic, and borderline). Needle sharing carries a risk of contracting HIV. Psychiatric, mainly depressive, symptoms are common in dependent users. ‘Roid rage’ is the slang term for anabolic steroid-induced violent behaviour. ‘Muscle dysmorphia’ is a term applied to a type of dysmorphophobia where the person is unreasonably dissatisfied with their musculature. Withdrawal symptoms include reduced sex drive, fatigue, depression, dissatisfaction with body image, headaches, physical violence, angry and hostile feelings, manic or psychotic episodes, and a desire for more steroids.

Possible complications of anabolic steroids (e.g. Perry & Littlepage, 1992, Arvary & Pope, 2000)
 Acne, gynaecomastia, testicular atrophy, oligospermia, infertility in men
 Menstrual irregularity/amenorrhoea, clitoral hypertrophy, deep voice, hirsutism, facial hair, male-pattern baldness in women
 Premature closure of growth plates (short stature) in adolescents
 Hypertension, atherosclerosis, increased low-density lipoproteins, decreased high-density lipoproteins, myocardial infarction, CVA
 Cholestatic hepatitis, oesophageal varices
 Renal, hepatic, and prostate neoplasia
 Anaesthetic problems
 Avascular necrosis of the femoral head
 Gateway to other drugs, e.g. opioids

Interestingly, men appear to want more muscle and believe that women want them to have more muscle, whereas women do not find big muscles so attractive in their men!(Pope ea, 2000)

Examples of commonly used anabolic steroids **(after Rashid ea, 2007)**

Oral – methenolone acetate, methandrostenolone, oxandrolone, oxymetholone, stanozolol
Intramuscular – boldenone undecenoate, methenolone acetate, Sustanon 250 (4 esters of testosterone), testosterone enanthate or cypionate

Opiates suppress activity of the hypothalamic-pituitary-adrenal (HPA) axis, with decreased secretion of ACTH and cortisol. They also induce a blunting of the response to CRF, ACTH and stress, and a decreased response to metyrapone. Sudden opiate withdrawal leads to activation of the HPA axis a number of days after the last intake of drug. Glucocorticoid levels normalise with abstinence, although a blunted stress response and increased glucocorticoid feedback may persist for long periods. Acute cocaine intake increases glucocorticoid secretion, this effect decreasing with chronic exposure. Abrupt cessation of heavy cocaine intake also increases glucocorticoid secretion, but this promptly normalises with abstinence. Suppressed cortisol response to stress occurs in abstinent cocaine addicts unless when craving for cocaine is induced.(Piazza & Aouizerate, 2002)

Acute and chronic ingestion of alcohol increases glucocorticoid secretion²⁴⁴⁷ and secretion increases further during withdrawal but normalises quickly during abstinence. Glucocorticoid secretion is increased by intense cigarette smoking, tolerance to this effect often appearing with chronic nicotine intake; cortisol levels rise when a heavy smoker ceases his habit; abstinence leads normalisation (and even an eventual drop in) of cortisol levels.

²⁴⁴⁷ Leading in some cases to a pseudo-Cushing’s syndrome.

Erythropoietin

Erythropoietin, a doping agent, may cause polycythaemia, hypertension, myocardial infarction, cerebral sinus thrombosis and other cerebrovascular disease.(Lippi ea, 2006)

Caffeine²⁴⁴⁸

The central pharmacological effects of the methylxanthines (cardiac stimulation, diuresis, bronchodilation, and central nervous system activation), such as caffeine, involve competitive antagonism at adenosine (an inhibitory amino acid) P₁ receptors (meprobamate blocks reuptake of adenosine and acts as an adenosine agonist, causing sedation). This results in an increase in intraneuronal cAMP phosphodiesterase (a second messenger that augments the actions of many hormones and neurotransmitters, such as noradrenaline).

Coffee and tea, though not caffeine itself, substantially reduce phenothiazine absorption. Caffeine antagonises BZDs. Caffeine- (or halothane-) induced contraction of muscle tissue *in vivo* is employed in the standardised test for malignant hyperthermia.

Caffeine (125-2000 mgs.) given intravenously five minutes before each application of bilateral electroconvulsive therapy (ECT) decreases the seizure threshold with no loss of clinical efficacy and with a reduction in the stimulus intensity required.²⁴⁴⁹

Suddenly stopping even a relatively low caffeine intake may give rise to headache, fatigue, reduced vigour, dysphoria (increased scores on Beck Depression Inventory), and drowsiness that begin within 12-24 hours, peak at 20-48 hours, and last for about 7 days. Symptoms may be mild to severe, and use of unauthorised medications, such as BZDs, may increase. An intake of two or more servings of caffeinated beverages per day may place one at risk for withdrawal symptoms.

Symptoms of caffeine poisoning (affects up to 10% of population)

- Restlessness
- Anxiety
- Irritability
- Agitation
- Muscle tremor
- Insomnia
- Headache
- Sensory phenomena - tinnitus, lightheadedness, light flashes
- Diuresis
- Cardiovascular symptoms - tachycardia and abnormal rhythms
- Gastrointestinal problems - nausea, vomiting and diarrhoea

Overdose of caffeine (> 10 cups of strong coffee)

- Insomnia
- Restless excitement

²⁴⁴⁸ A stimulant,(O'Shea & Yek, 2002; Winston ea, 2005) caffeine is found in tea, coffee, soft drinks such as cola, and various prescription and non-prescription medicines. It is the most widely used psychoactive drug worldwide and in excess is unhealthy. The status of 'functional' or 'stimulant' soft drinks, containing taurine (2-aminoethane sulphonic acid), glucuronolactone, such as 'Red Bull', remains worrying, including a risk for stroke. Caffeine has a half-life of about 5 hours. Purine receptors, e.g. adenosine receptors, are divided into P₁ and P₂ subtypes (A₁ and A₂). If a patient is drinking lots of coffee to counter sedation from medications such as anticonvulsants it may be possible to replace caffeine with modafinil.

²⁴⁴⁹ However, using caffeine and right unilateral ECT, no change has been found in convulsive threshold. Problems include anxiety, agitation, nausea, retching, and prolonged seizures. There is a risk of cardiac dysrhythmia, mainly in the elderly and those with pre-existing cardiac disease. However, moderate use probably has no adverse cardiac effects. The present advice is not to give caffeine pre-treatment before ECT.(Scott, 2005, p. 113) The xanthine theophylline, which also lowers seizure threshold (and blocks P₁ receptors), can lead to status epilepticus which given with ECT. Therefore, theophylline should be stopped or given in as low a dose as is clinically feasible during ECT. Anyway, a small dose of phenothiazine given several hours before ECT may be effective in reducing seizure threshold.

- Tachycardia
- Muscle tension
- Vomiting, delirium and seizures (severe cases)

There may be a role for caffeine in producing cardiovascular disease, but methodological problems disallow firm deductions. Ground coffee brewed by mixing it with hot or boiling water may increase the serum cholesterol level, an effect that is substantially reduced by filtering, but caffeine may not be the culprit. Cancer links (e.g. pancreatic) remain unproven since many subjects smoke tobacco. There is a possible link with fibrocystic disease of the female breast, but some research suggests reduced breast cancer risk in women with BRCA1 or 2 mutations who consume at least 6 cups of coffee a day. Caffeine increases gastric acidity and is best avoided in people with peptic ulcer disease. A 30-year follow-up of 8,000 Japanese–American males (Honolulu Heart Program) singled out caffeine itself (independent of tobacco smoking status) as being associated with a reduced incidence of Parkinson’s disease. (Ross ea, 2000) Animal studies have linked caffeine with birth defects. Wisborg ea, (2003) in a prospective Danish study, found that heavy coffee intake during pregnancy was associated with having a stillbirth (8 or more cups of coffee per day increases the risk to twice that where no coffee is consumed) but not with death of the baby during the first year of postnatal life. Earlier, Cnattingius ea (2000) had reported that caffeine use may increase the risk of spontaneous abortions in early pregnancy. Whilst maternal caffeine intake negatively correlates with the baby’s birth weight, it has been argued that this applies only to mothers who also smoke cigarettes. Whilst the CARE Study Group (2008) found that caffeine restricts fetal growth, not all studies show that reducing caffeine intake has an effect on birth weight or length of gestation. (Bech ea, 2007)

Caffeine causes insomnia, especially in the older person.

Some causes of early morning wakening

Depression
Alcoholism
Anorexia nervosa
Caffeine

Caffeine can worsen many psychiatric symptoms, especially panic. Caffeine given under double-blind conditions made psychotic symptoms worse in schizophrenia. (Lucas & Pickar, 1990) There are connections between adenosine A2A receptors and the brain dopaminergic system: adenosine inhibits dopaminergic transmission and therefore blockade of adenosine A2A receptors by caffeine may increase activity of DA, leading to worsening of psychosis. (Ferre ea, 1992) Sudden cessation of caffeine intake can increase serum lithium levels by about 24%. Caffeine exaggerates the tremor of lithium.

The management of excessive coffee consumption is based on education, a stepwise reduction in intake over 1-2 weeks, and a final goal of a more acceptable intake. Caffeine is contraindicated in panic disorder. Caffeine pre-treatment for patients undergoing ECT remains an unsettled issue: side effects may necessitate lowering the dose of caffeine, and prolonged seizures require medical intervention.

Nicotine & tobacco

‘Every year 5 million people die from tobacco-related diseases, the world’s major preventable cause of death and disease’. (Arnott ea, 2008)

Nicotine is a highly addictive alkaloid from the leaves of the tobacco plant, *Nicotiana tabacum*. Of course, tobacco contains more chemicals than nicotine²⁴⁵⁰. Cigarette smoking induces the metabolism of many drugs so that cessation or curtailment of smoking (e.g. during hospital stays) may cause raised serum concentrations and side effects of such drugs (e.g. clozapine).

²⁴⁵⁰ Nicotine is not a recognised carcinogen or a cause of COPD but addiction to nicotine is the main reason for continued smoking.



Nicotiana tobacum

Fifty years after the Doll and Hill (1954) study of mortality among male British doctors who smoked, Doll et al (2004) reported that such men who were born during 1900-30 and who smoked died an average of 10 years earlier than non-smokers; over half of young doctors who continued to smoke during the 1950s would die as a result of smoking; among those born in 1920, prolonged smoking increased the age specific mortality three times; stopping smoking aged 50 years halved the risk; and stopping at 30 years of age almost returned the risk to that of non-smokers.

Tobacco use is the single most important preventable cause of death and disease in the western world, accounting for 19% of all deaths in the USA in 1990 and claiming more lives worldwide than war.

1991

European Community: 44% of men and 28% of women smoked

Britain: Over half a million British children aged 11-15 years partook of tobacco

USA: one-third of men and one-quarter of women smoked²⁴⁵¹

British GPs: 10% of were smokers

UK: 300 people died daily in the because of tobacco

Over 430,000 and 4.2 million died annually in EC and worldwide respectively

According to Edwards (2004) the decline in smoking in the UK may have ended – since 1994 the prevalence among adults remained at about 28%. This negative prognostication does not seem to be true since only 23% of men and 21% of women were smokers in 2006, with a decline in British smokers over 16 years of age from 24% in 2005 to 22% in 2006.(Creagh, 2008)

Nicotine is not the main component of cigarette smoke that accounts for the bulk of premature morbidity and mortality, but rather the 40-plus carcinogens and other toxic materials that are inhaled with it (Kawachi, 2003)

About a quarter of all persistent smokers in India are killed by their habit before age 70 years, losing about 20 years of life expectancy (Gajalakshmi et al, 2003)

Despite overall decline of the habit in countries such as the USA, many people continue to smoke

2001: Lifetime prevalence of nicotine dependence was estimated at 24%, and more women around the globe were taking up the habit
About 100,000 people die each year in UK due to of tobacco-related illnesses, the figures for the Irish Republic being 17,038, 16,790 and 15,329 for the years 1990, 1995, and 1999 respectively

Percentages of males and females who smoked in Britain in 1972, 1982 and 1984 were 52, 38, 36 and 42, 33, 32 respectively, although more girls than boys were smoking in 1996

31% of adults in the UK smoked in 1991 – the same percentage of adults as now smoke in Ireland

35% of Irish people aged 15-17 years smoke, and one in five of those aged 9-17

Presently, about 13 million people in the UK are regular smokers

2008: US Congress debates legislation to have tobacco regulated by FDA

2008: The prevalence of smoking among Cork bar workers was very high before smoke-free workplace legislation (Mullally et al, 2008)

2009: According to the British Household Survey for 2007 the prevalence of smoking had fallen to 21% (highest rate of smokers = 20-24 year-old age group) (Mashta, 2009)

2009: US Senate passage of legislation allowing FDA to strongly regulate cigarettes and other tobacco products; ban on smoking within 1,000 feet of schools/playgrounds and tobacco-brand sponsorship of sports/entertainment; President Barack Obama signed *Family Smoking Prevention and Tobacco Control Act of 2009* in June giving FDA broad authority to regulate tobacco products

2009: Tobacco hidden from view in retail outlets

2009: EU survey finds 33% of people in Ireland smoke (was 33%, 27%, and 29% in 1998, 2002, and 2007 respectively)

2010: Eurobarometer study of European Commission: 29% of Europeans smoke and 49% never smoked; 38% and 16% allow smoking at home and in the family care respectively; circa one in 4 are exposed to tobacco smoke in the workplace

²⁴⁵¹ In 1991, 73% of Americans ever smoked; 27% currently smoked – contrasting with 85% and 51% respectively for alcohol use. In 2007 and 2008 19.7% and 20.9% of US adults were current smokers, the increase being due perhaps to stresses of economic recession but in the face of massive increases in federal tax on cigarettes.(Barclay, 2009)

A German study of 18-65-year-olds found a 36.2% prevalence of current smokers and a one-year prevalence of nicotine dependence of 9.4%. (Schmitz ea, 2003) Adolescent females were the only group who showed an increase in smoking incidence in the UK in 1991. Smoking is very common in psychiatric patients in all settings, but recording of smoking habits and intervention by medical personnel are uncommon. The High Court in England and Wales, when deciding on an appeal by patients at Rampton in 2008, decided that there is no absolute right to smoke in ones place of abode and that staff are not obliged to arrange for smoking areas²⁴⁵². (Ratschen ea, 2008) Some staff in psychiatric units fear that patients' might become more ill if not allowed to smoke. (Praveen ea, 2009) Poorer countries are targeted for sales when home markets contract and major cigarette producing nations are unlikely to wholeheartedly support international tobacco control agreements. Poorer countries have more smokers, e.g. 73% of males in Vietnam smoke. (Edwards, 2004) Poorer people in general and more likely to smoke than are richer people.

Cost: Lost productivity in the US due to smoking-related mortality averages \$92 billion annually. Health care costs of smoking in the US amount to \$75 billion per year. (Anonymous, 2007)

Aetiology: Availability is crucial to aetiology, especially among the young. (Hanrahan, 2002; Dobson, 2005) Most starters are in their early teens and commence smoking for psychosocial reasons²⁴⁵³. The aversive hurdle of the first cigarettes has to be overcome. The great majority will later regret having started to smoke. Factors associated with adopting the habit of smoking include extraversion, a wish to emulate 'adult' behaviour, risk-taking²⁴⁵⁴, using larger quantities of other drugs²⁴⁵⁵ than non-smokers, lower socio-economic status, smoking by peers, relatives or idols, advertising²⁴⁵⁶, and, perhaps, a modest hereditary element. (Lessov ea, 2004) Adolescents are at high risk of smoking if their parents started to smoke when young and reached high intake quickly and were persistent smokers. (Chassin ea, 2008) Nicotine withdrawal leads to anxiety, restlessness, insomnia, irritability, sweating, poor concentration, listlessness and depression. (Jarvis, 2004) The body may take a long time to adjust to cessation of nicotine intake. One theory behind the need to continue smoking considers this physical addiction model. (Jarvis, 2004) Another theory centers on the ability of the smoker to control his level of arousal, such as decreasing it and so reducing the effects of stress or increasing it and so maintaining vigilance. The latter overcomes the effects of monotony and increases the selectivity of attention. Displacement of aggression may be important. There is some tentative evidence that female non-smokers may be calmed by acute nicotine inhalation, with anxiety and aggressiveness being evoked in male comparators. The exact relationship between nicotine and anxiety has been the subject of conflicting findings, some workers suggesting that smoking may be an aetiological factor. A positive relationship between family and personal smoking habits may be explained in terms of nature and/or nurture. The relationship with education varies between cultures, being associated with lower education in Britain but higher education in southern Europe. Tobacco revenue²⁴⁵⁷ is considerable²⁴⁵⁸. Reduced consumption following a shift to jobs outside the tobacco industry is unlikely to increase unemployment rates as much as the tobacco industry suggests. The difference between financial solvency and destitution for many pensioners relates to smoking status.

Patients with histories of major depression or anxiety disorders may experience particularly severe abstinence symptoms when withdrawing from tobacco.²⁴⁵⁹ Schizophrenic patients have very high rates of cigarette smoking, and may be at greater risk for tardive dyskinesia because of it. It has been suggested that patients with schizophrenia smoke to decrease their negative symptomatology, perhaps because of a primary central nicotinic defect that leads to abnormal sensory gating, or to transiently normalise the P50 so as to better enable them to filter incoming stimuli. Male adolescents have been found to smoke more than comparison subjects before they develop schizophrenia. (Weiser ea, 2004) Alcoholics smoke excessively as a group; in fact, more alcoholics die because they smoke than because they drink.

²⁴⁵² Nurse escorts would be required for outdoor smoking.

²⁴⁵³ Peer pressure, media, and esteem.

²⁴⁵⁴ E.g. not using seat belts.

²⁴⁵⁵ Such as coffee and alcohol.

²⁴⁵⁶ Including smoking in movies. (Sargent ea, 2001; Dalton ea, 2003)

²⁴⁵⁷ Prized by Napoleon III who challenged others to come up with an equally lucrative "vice".

²⁴⁵⁸ Yielding, e.g., IR£440 million (IR£330 m excise duty plus IR£110 m VAT) for the Irish exchequer in 1990. Cigarettes involve a \$47 billion market in the USA, \$3 billion less than it costs to treat their medical consequences. The Japanese government owned two-thirds of the nation's tobacco in 2003, a fact which may explain its tardiness in tackling the problem. (Watts, 2003)

²⁴⁵⁹ Neuroticism may be a factor in the predisposition to both of these psychiatric disorders and to smoking. Fergusson ea (2003) and Benjet ea (2004) argue for a link between smoking and depression, but admit that the direction of causality remains unknown.

Addiction potential: The modified Fagerström test for nicotine dependence (Heatherton *et al.*, 1991) is commonly used. A maximum score of 10 indicates greater dependence. Relapse is best predicted by number of cigarettes smoked and how long before smoking the first cigarette of the day.

Modified Fagerström test for nicotine dependence

- How soon after waking do you smoke first cigarette? – score 3, 2, 1, and 0 for < 5 minutes, 6-30 minutes, 31-60 minutes, and > 60 minutes
- Do you find it hard to refrain from smoking in no-smoking areas? – 1 for yes, 0 for no
- Which cigarette would you hate most to give up? – 1 for first in the morning, 0 for the rest
- Number of cigarettes smoked daily? – 0 for 10 or less, 1 for 11-20, 2 for 21-30, 3 for higher
- Do you smoke more frequently during the first hours after waking than during the remainder of the day? – 1 for yes, 0 for no
- Do you smoke if so ill that you are in bed most of the day? – 1 for yes, 0 for no

Possible sources of reward in smoking can be divided into three main areas: sensory²⁴⁶⁰, social²⁴⁶¹, and pharmacological. A variation in the nicotine receptor may be associated with excessive smoking and reduced likelihood of quitting. Cannabis use is more common among young cigarette smokers. The tobacco industry appears to be not beyond utilising the popular image of drug abuse among its customers: as when, for example, they give out free key rings with a concealed vial attached. It has also attempted to neutralise anti-smoking legislation and has hired scientists to misrepresent the facts. (e.g. Hong & Bero, 2002; Ramsay, 2002; Hammond *et al.*, 2006) Smokers exposed to smoking cues cause similar changes on PET-scanning to those found with other addictive substances: there is a significant positive association between craving and metabolism in the orbitofrontal cortex, the dorsolateral prefrontal cortex, and the anterior insula. (Brody *et al.*, 2002)

Pharmacology: One definition of a smoker is that the carboxyhaemoglobin concentration in the blood is equal to or greater than 2% (normally < 1.5% in a non-smoker), or the nicotine breakdown product cotinine²⁴⁶² concentration is equal to or greater than 50 nmol/L. Yudkin *et al.* (2003) confirmed abstinence on the basis of a salivary cotinine concentration of at the most 20 ng/ml or an expired carbon monoxide of 10 ppm or less. Use of store second trimester maternal blood in Scotland to measure cotinine revealed that self-reported smoking by pregnant women underestimated smoking status by 17%. (Shipton *et al.*, 2009) Nicotine in cigarette smoke reaches the brain in ten seconds (or less), faster than when given intravenously. (Kawachi, 2003) Rats will press levers to obtain water containing minute concentrations of nicotine at a faster rate than for water devoid of the chemical.

Nicotine releases noradrenaline and dopamine in the animal brain, and increases dopaminergic activity in human basal ganglia. It is possible that one or both of these transmitters may activate limbic pathways. It is thought that activation of nicotinic acetylcholine receptors in the ventral tegmental area triggers DA release in the nucleus accumbens. Results of various studies suggest that heritable predisposition to smoking may be partly mediated by genetic variation in DA receptors and its transporter. (e.g. Audrain-McGovern *et al.*, 2004) Tyrosine hydroxylase and alpha-2-adrenoceptors are reduced in the locus coeruleus of chronic smokers. Nicotine reacts with some acetylcholine (ACh) receptors but it sticks to the receptor for a long time. Hence the initial effect is ACh-like, but thereafter it blocks the action of ACh. By changing certain aspects of smoking behaviour, such as depth and duration of inhalation, smokers exert some control over the stimulation/inhibition ratio.

It appears that higher availability of the beta-2 subunit (beta-2*-nAChR) of the nicotinic acetylcholine receptor persists for up to a month after stopping smoking and returns to non-smoking levels by 6-12 weeks of abstinence. (Cosgrove *et al.*, 2009)

Smoking significantly inhibits brain MAO-A and -B. Smoking one cigarette does not have this effect. It is therefore surmised that this action is not due to nicotine.

Rats who receive nicotine by continuous infusion will develop withdrawal signs when given naloxone. Morphine will attenuate withdrawal signs in rats when nicotine infusion is terminated. Therefore, opioid systems may be involved in dependence on nicotine, at least in the rat. (Malin *et al.*, 1993)

²⁴⁶⁰ Olfactory, gustatory, and visual effects; ritual handling; orality.

²⁴⁶¹ Social image; displacement of affect onto ritualised activity; associated interpersonal activities.

²⁴⁶² CYP2A6 is involved in metabolism of nicotine and cotinine.

Intravenous nicotine acts on the nucleus accumbens (dopamine release), amygdala, cingulate and frontal lobes, as do cocaine, amphetamine and opiates, areas that are important for the reinforcing, mood-elevating and cognitive properties of such chemicals. PET data suggest that nicotine increases normalised rCBF in the left frontal region and decreases rCBF in the left amygdala; and that the rCBF in the right hemisphere reticular system is related to nicotine dose in an inverted U-shaped pattern and is strongly related to craving/addiction. (Rose ea, 2003) An fMRI study (Hong ea, 2009) suggested that severity of nicotine addiction is associated with the strength of dorsal anterior cingulate cortex-striatal circuits (not modified by nicotine patch) whereas short-term administration of nicotine increased cingulate-neocortical functional connectivity patterns (suggesting a role in cognitive enhancement).

Nicotine withdrawal is the most common abstinence syndrome in intensive care units. Wider swings in alpha wave activity on the EEG are seen in cigarette smokers (decreased when relaxed, increased when stressed) than in controls. Heavy smokers may need bigger doses of psychotropic drugs because cigarette smoke induces hepatic enzymes²⁴⁶³ so that, e.g., plasma tricyclic antidepressant levels are lowered and schizophrenic patients may need higher doses of clozapine, olanzapine and many typical neuroleptics. Similarly, psychotropic toxicity may follow smoking cessation. So-called 'low yield' cigarettes can probably deliver as much tar and nicotine as 'higher yield' versions. (White, 2002) The shift to low tar cigarettes may account for an increase in adenocarcinoma, i.e. low tar smokers may inhale more deeply, the smoke now reaching peripheral pulmonary areas where that tumour arises. Harris ea (2004) found that the increase in lung cancer risk is similar in people smoking medium (15-21 mg), low (8-14 mg) and very low (7 mg or less) tar cigarettes, and people who smoke non-filtered cigarettes with tar ratings of at least 22 mg have an even higher risk of lung cancer.²⁴⁶⁴

Some adverse effects of smoking

Cancer - lung²⁴⁶⁵, oro-pharynx²⁴⁶⁶, larynx, oesophagus, pancreas, breast²⁴⁶⁷, bladder

Risk factor for macular degeneration (Mitchell ea, 2002; Kelly ea, 2004), ophthalmopathy in Grave's disease, vascular dementia, stroke, and other cardiovascular diseases, including acute myocardial infarction²⁴⁶⁸ (Teo ea, 2006) and acute recurrent and chronic pancreatitis (Yadav ea, 2009)

May be an independent risk factor for non-insulin dependent diabetes mellitus²⁴⁶⁹ and age-related cataract

Increased susceptibility - acute coryza, chronic bronchitis/emphysema (COPD), TB, other respiratory diseases²⁴⁷⁰, and peptic ulcer

²⁴⁶³ CYP450-1A2.

²⁴⁶⁴ The EU stated that it would ban all statements like 'light', 'low tar' and 'mild', and from January 2004 the tar content of cigarettes would be reduced from 12 to 10 mgs and a ceiling of 1 mg would apply for nicotine. Gray and Boyle (2004) state that figures for tar, nicotine, and carbon monoxide are misleading and call for their removal. A US federal judge ruled in 2007 that tobacco companies cannot use words like 'light' or 'low tar' to sell outside the US. (Harding, 2007)

²⁴⁶⁵ This is now the chief cause of cancer-related death in American females. British lung cancer deaths overtook deaths from TB in 1952: 14,000 v 9,000. Age-standardised death rates per 100,000 population from lung cancer in Ireland in 1996 were 62, 25 and 42 for men, women and in total respectively, compared to EU average of 70, 15 and 38 and UK figures of 70, 31 and 47 [Croatia, Hungary and Poland had very high figures for males whilst the Iberian countries had particularly low figures for women.]. (Brennan & O'Connor, 2003, p. 27) A study of lung cancer mortality in the EU (Didkowska ea, 2005) found it to be higher in central and eastern areas than in western parts and, for each sex, to be particularly higher in Hungary; the rate was declining in middle aged men in all new EU states but was still increasing among women in most countries in the EU.

²⁴⁶⁶ Increasing in American women because of increase in snuff use and chewing of tobacco. Bangladeshis living in the UK often chew tobacco. Young people of south Asian origin in UK are using more (cheap) smokeless tobacco products. Smokeless tobacco may cause a small increase in risk of fatal MI and CVA. (Boffetta & Straif, 2009) Important causes of oropharyngeal cancer include the alkaloids in *Areca catechu* (betel nut, *supari*) and tobacco (in cigarette, the chocolate cigarette known as bidis, through a hookah, or chewed as *gutka* [tobacco, betel nut, and other spices in colourful sachets] or *paan* [so-called because wrapped in green betel nut plant leaf – a paste may be added which may contain lime]). (Panesar ea, 2008)

²⁴⁶⁷ Timing in relation to parity and menarche may be crucial. (Band ea, 2002)

²⁴⁶⁸ Admissions for smokers and non-smokers with acute coronary syndrome declined in Scotland since the ban on smoking in enclosed public places in March 2006. (Pell ea, 2008)

²⁴⁶⁹ Both active and passive smoking may have a role in the development of glucose intolerance in young adulthood. (Houston ea, 2006)

²⁴⁷⁰ Whilst sarcoidosis may be less common in smokers, certain interstitial disorders are more common, e.g. idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis), respiratory bronchiolitis-interstitial lung disease, and desquamative interstitial pneumonia. (Innes & Reid, 2006, pp. 715 & 717) Smokers are less prone to hypersensitivity pneumonitis (extrinsic allergic alveolitis – smokers have a decreased antibody reaction to the antigen) but more prone to byssinosis and primary spontaneous pneumothorax than are non-smokers. (Innes & Reid, 2006, pp. 719, 720 & 733)

Rheumatoid arthritis (e.g. Sugiyama ea, 2010)
 Aphthous ulcers²⁴⁷¹
 Hypertrophic pyloric stenosis²⁴⁷² in infants
 Impotence²⁴⁷³, infertility²⁴⁷⁴, miscarriages, stillbirth, neonatal birth, reduced quality of breast milk, cleft lip/palate, and cervical cancer²⁴⁷⁵; in infants and children, passive smoking (among other factors) is blamed for SIDS (Kinney & Thach, 2009), respiratory infection (including TB), cognitive impairment (Llewellyn ea, 2009), and asthma²⁴⁷⁶
 Unclear cause-effect relationship with panic attacks
 Decreased response to treatment of mania.(Berk ea, 2008)
 Premature greying of hair may be an effect of smoking²⁴⁷⁷
 Smoking is associated with reduced bone mass, increased risk of osteoporotic fracture, diminished serum levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathormone, which may be independent of lifestyle
 Decease in financial resources, despite wide disparity of retail prices between countries
 Deaths may be increased from cirrhosis, suicide and poisoning, although associated alcohol abuse and personality factors contribute

Smoking does not protect against Alzheimer's disease (Mehta & Yaffe, 2002) but smokers are less likely to develop aphthous ulcers or to die from Parkinson's disease.(Doll ea, 1994a; Ben-Shlomo, 1996) Whatever the cause, smokers usually die younger than their peers do. The P3 component of visual event-related potential (ERP) is prolonged in current but not ex-smokers, whereas the P3 component of the auditory ERP has been reported as normal in smokers.(see Gamma & Liechti, 2002, for a review) Two thirds of women who stop smoking during pregnancy start smoking again after parturition.(Coleman, 2004a)

Passive smoking: The tobacco industry has engaged experts to state that passive smoking is either harmless or neutralised by ventilation²⁴⁷⁸.(Dobson, 2006) Large amounts of money are now being awarded for the victims of passive smoking, i.e. exposure to other people's smoke. The home is the main source of passive smoking for children and less than one in five parents in smoking households banned smoking in the home in a cross-sectional survey carried out in Coventry and Birmingham.(Blackburn ea, 2003) The family car provides an even more enclosed space for passively inhaling smoke. Non-smokers married to smokers are said to have three times as much cotinine in their blood as do those married to non-smokers. However, raised cotinine levels in non-smokers also reflects passive exposure at work, in pubs, and restaurants.(Jarvis ea, 1992)

Mortality rate is increased among adults living with smokers by 15%.(Hill ea, 2004; Wen ea, 2006) Jamrozik (2005) estimated that passive smoking in the UK was responsible for 617 deaths of employed persons per year²⁴⁷⁹ and 2700 and 8000 deaths per year from domestic exposure in people aged 20-64 years and those over 65 years respectively.

Smoking during pregnancy is given greater coverage elsewhere.

Adverse effects of passive smoking

²⁴⁷¹ Basically the aetiology is not known and autoimmunity may play a part. Some cases have haematinic deficiencies, bowel disease, or AIDS and some cases are related to the menstrual cycle. Smoking cessation and other stressors are also thought to be related.

²⁴⁷² There may be a connection between maternal smoking and this condition but there are methodological problems with such research: not all confounding variables are controlled for and it is not known whether it is smoking during or after pregnancy that is important.(Sørensen ea, 2002)

²⁴⁷³ Smoking is associated with erectile dysfunction in males, since smoking increases atherosclerosis of the penile arteries.(Kandel ea, 2001) It might reduce arousal in females.

²⁴⁷⁴ Women smokers reduce their chances of conceiving by up to 40% each month. Smoking couples are less responsive to infertility treatment. Smoking has a mild but negative effect on spermatogenesis, and may contribute to infertility, e.g. if a man has a varicocele, and impotence.

²⁴⁷⁵ Smoking damages epithelial DNA in the cervix uteri.

²⁴⁷⁶ A BMA report (*Smoking and Reproductive Life: The Impact of Smoking on Sexual, Reproductive and Child Health* – www.bma.org.uk)

²⁴⁷⁷ We know that smoking shortens the telomere.(Valdes ea, 2005)

²⁴⁷⁸ In Germany, the tobacco industry stopped Lufthansa from banning smoking on domestic flights in the early 1990s.(Tuffs, 2008)

²⁴⁷⁹ Including 54 in the hospitality industry.

Lung cancer and other respiratory disease²⁴⁸⁰

Coronary heart disease (Whincup ea, 2004; McGhee ea, 2005)

Death from acute myocardial infarction (Teo ea, 2006) and stroke (Bonita ea, 1999; McGhee ea, 2005)

Stroke risk increased in non-smoking spouse (Glymour ea, 2008)²⁴⁸¹

Children of parents who smoke have high urinary cotinine levels as well as upper respiratory and hearing problems, exacerbations of asthma, sudden death in infancy (SIDS)²⁴⁸², and, possibly, brain tumours

Stopping smoking: Currie ea (2010) found that intensive smoking cessation services in Ireland in 2006 used evidence-based interventions but lacked uniformity and consistency. Smokers have become increasingly socially marginalised (Christakis & Fowler, 2008) but the marginalised cannot be forgotten. (Schroeder, 2008) Motivation to quit the habit is crucial, (West, 2004) and unplanned quit attempts may be successful. (West & Sohal, 2006) However, there is evidence that 'quit-success' genes exist. (Uhl ea, 2008) Although often unaware of their patients' smoking habits and not as interventionist as they might be, medical practitioners can influence a few smokers to quit, with large public health benefits. Smoking among doctors is common in China, Bosnia-Herzegovina, Chile and Russia but is rare in India, Australia, Iceland, Sweden and the UK. (Jamrozik, 2004a) Approaches aimed at quitting are many in number.²⁴⁸³ According to Rigotti (2002), bupropion and nicotine replacement may be equally efficacious.

Strategies for individual cases include

Contingency contracting²⁴⁸⁴ - monetary consequences of relapse

Set target date

Change to weaker brands

Keep record of number of cigarettes smoked

Nicotine fading - slowly cutting down

Avoid/change cues for smoking

Coping skills training

Take more exercise

Nicotine replacement therapy (NRT) is subject to much greater regulation than cigarettes (Kawachi, 2003), a position that needs to be reversed. (Mayor, 2007) Whilst the RCT evidence is that NRT is effective in helping people to quit smoking (Moore ea, 2009) it has been difficult to tease out the contribution of NRT from the support derived from regular contact with a professional. However, Piper ea (2009) conducted a double-blind RCT of nicotine lozenge, nicotine patch, nicotine patch plus lozenge, sustained-release bupropion, bupropion plus nicotine lozenge, or placebo, all participants receiving 6 individual counselling sessions; only the nicotine patch plus nicotine lozenge produced significantly higher abstinence rates at 6 months after quitting than did placebo.

²⁴⁸⁰ Methodological problems may make it difficult to attribute lung cancer to passive smoking and negative findings are controversial. (Smith, 2003; Enstrom & Kabat, 2003; Wise, 2008) but lung cancer risk is most likely greater if a spouse smokes. (Anonymous, 2002) Vineis ea (2005) conducted a prospective study using cotinine measurements and concluded that environmental tobacco smoke is a risk factor for lung cancer and other respiratory diseases, especially in ex-smokers. This is supported by evidence from Hong Kong. (McGhee ea, 2005) Blackburn ea (2003) found that banning smoking in the home led to a small but significant reduction in urinary cotinine to creatinine ratio in infants. Women with glutathione-S-transferase M1 deficiency due to gene deletion may not be able to detoxify certain carcinogens and so become more at risk from passive smoking. Work done in China suggested a connection between passive smoking at home and at work and COPD and respiratory symptoms, although a causal relationship could not be proven. (Yin ea, 2007)

²⁴⁸¹ Whincup ea (2004) failed to find any consistent association between cotinine concentration and stroke.

²⁴⁸² Smoking father doubles risk; smoking mother quadruples risk; both parents smoking increases risk 5 times.

²⁴⁸³ These can be summarised thus: behavioural (electric shock aversion or getting someone to smoke very quickly until nauseated; relaxation exercises, systematic desensitisation; programmed smoking and contract management with the exercise of self control), which are relatively disappointing; drugs (see table); acupuncture, hypnosis, sensory deprivation, and various forms of counselling and psychotherapy, including telephone helplines such as "Smokeline" in Scotland.

²⁴⁸⁴ Contingency management is particularly effective for substance misuse according to a meta-analysis. (Dutra ea, 2008)

In real life, few smokers receive combined pharmacotherapy and psychosocial therapy. (Kay & Tasman, 2006, p. 473) Women with the variant T allele of the D2 receptor DRD2 32806 may be more likely to benefit from nicotine patches than those with the more common CC genotype. (Yudkin ea, 2004)

Drugs used to aid smoking cessation

(a) Nicotine preparations to aid smoking cessation

*Chewing gum**: contains nicotine (N) in buffered resin - released N absorbed through buccal mucosa.

Vigorous chewing causes gastrointestinal upset. Try smaller 2 mgs size initially. Long-term dependence on the gum can occur; 5-10% using it after one year. Side effects include transient oro-pharyngeal irritation, nausea, flatulence, hiccups, and aggravation of dyspepsia.

Transdermal patch e.g. Nicorette (Invisipatch), Nicotil, NiQuitin. Place on side of chest. Skin reactions include erythema, oedema, and pruritus. The strength of patch varies from 5 to 30 mg depending on the preparation.

*Nasal spray**. Quick absorption: useful for heavy smokers. Can cause short-lived nasal and throat irritation, sneezing, cough and watery eyes. Dose: 2 sprays/nostril/hour for 16 hours/day, decreasing dose over about 3 months.

*Inhaler**. Holder and cartridge set. Can cause throat irritation and cough. Effective.

*Microtabs**. Placed under tongue, dissolving over 20-30 minutes. If you smoke at least 20 cigarettes/day use 1-2 tablets/hour to relieve cravings.

Lozenges. Nicopass, 1.5 mg in fresh mint and liquorice mint flavours. Niquitin lozenges have been advertised for those wishing to decrease cigarette consumption one at a time.

NicoShot: The German company Nautilus announced in 2005 that it was developing a beer containing 3 mg nicotine and 6.3% alcohol!

*e.g. Nicorette

(b) Mecamylamine, a nicotine antagonist, may have a role in blocking the rewarding effect of nicotine and thereby reducing craving. (Lancaster ea, 2000)

(c) Cytisine, a high affinity agonist for the $\alpha 4\beta 2$ nicotinic receptor and alkaloid found throughout C.

laburnum, has been used for decades for smoking cessation in Eastern Europe. Although trials have been of poor quality, it may be effective. (Elter, 2006)

According to Nides ea (2006) the $\alpha 4\beta 2$ nicotinic partial agonist varenicline tartrate (Champix) appeared to be effective in the long and short term²⁴⁸⁵. The aim is to reduce craving, withdrawals and, if one smokes, pleasure from that act. However,

Varenicline²⁴⁸⁶ (Champix)

Use in adults (> 18) only; avoid in pregnancy; only give during breastfeeding on risk-benefit analysis basis

Dose: start 1-2 weeks before quitting smoking; first 3 days 0.5 mg once daily; days 4-7 0.5 mgs twice daily; then 1 mg twice daily for 12 weeks (prolonged use does not appear beneficial: Anonymous, 2008e); consider tapering dose

Side effects: abnormal dreams/insomnia/somnolence/fatigue/dizziness, headache, nausea²⁴⁸⁷/abdominal discomfort or distension/flatulence/dry mouth/ vomiting/constipation/diarrhoea/increased appetite, dygeusia (distorted taste function)

Exercise caution: driving, machinery

Reports of depression that may include suicidal thoughts and behaviour in patients attempting to stop smoking with varenicline²⁴⁸⁸ (Anonymous, 2008e; Irish Medicines Board, 2008); also reports of psychosis in patients with mood disorder history and withdrawal-related psychosis. (Laine ea, 2009)

(d) Bupropion²⁴⁸⁹ (Zyban, 150 mg tabs)

This is structurally related to the appetite suppressant diethylpropion. It is recommended that the dose starts at 150 mg/day for 6 days, increasing to 150 mg twice daily with at least 8 hours between doses, the smoker giving up smoking during the second week of treatment. Sustained-release form effective in placebo-

²⁴⁸⁵ It performed better than placebo and bupropion but it is unclear how it compares with nicotine replacement. (Anonymous, 2008e)

²⁴⁸⁶ Pronunciation: va-re-nik-leen.

²⁴⁸⁷ Nausea is common.

²⁴⁸⁸ Smoking cessation *per se* may account for much of this. Gunnell ea (2009), although aware of methodological issues, found no clear evidence for a connection between varenicline and self-harm, fatal or non-fatal, compared with other smoking cessation products. However, prescribers of varenicline (or bupropion) should remain cautious. (Lavigne, 2009)

²⁴⁸⁹ British approved name is amfebutamone.

controlled, double-blind study; carbon monoxide in breath analysed for compliance check; usually minimal side-effects (dry mouth, insomnia, dreams, and seizures in 1 in 1,000 cases on 300 mgs/day; rarely causes serum sickness-like illness or psychosis – Michels & Marzuk, 1993); no weight gain; effect independent of depression; may be usefully combined with nicotine patch.

Bupropion studies have included intensive behavioural support, which raises efficacy questions about it or any other agent used alone. Absolute cessation rates are small. Bupropion may work by increasing dopamine concentration in nucleus accumbens. It may attenuate weight gain following cessation of smoking. It should be avoided if there is a risk of seizures (e.g. alcohol abuse or withdrawal, brain tumour, head trauma, eating disorder [electrolyte imbalance from starvation/purgation], antipsychotic medication [but Tsoi *et al.* {2010} found in a meta-analysis that bupropion reduced smoking rates in schizophrenia without harming the mental state], antidepressants, theophylline, and benzodiazepine withdrawal), during pregnancy, if there is anorexia or bulimia nervosa, if there is a history of bipolar disorder, or within 2 weeks of taking a MAOI. Concerns have been raised about both bupropion and varenicline and possible self-harm/suicide. (see Lavigne, 2009) Metabolised by CYP 2B6 – can prolong action of certain antidepressants (e.g. desipramine, paroxetine), 1c antiarrhythmics like propafenone and flecainide, and antipsychotics such as risperidone and thioridazine.

(e) Other antidepressants, especially nortriptyline, seem to be effective in helping people stop smoking. (Roddy, 2004; Aveyard & West, 2007) However, there appears to be no extra benefit from adding nortriptyline to nicotine replacement. (Aveyard *et al.*, 2008) SSRIs do not seem to be effective. (Hughes *et al.*, 2007)

Published studies of hypnosis show success rates ranging from 13% to 64% for smoking cessation; self-hypnosis training is stressed by practitioners, and a form of ‘cognitive restructuring’ is used by the client tempted to smoke: thoughts of harming body, quality of life, life span. Hypnosis appears to help some individuals, even if no more effectively than other effective measures or even no intervention. (Weinberger *et al.*, 2008, p. 433) but few trained practitioners are available.

A rare possibility is the occurrence of myocardial infarction if one smokes while wearing a patch, although most people have no increase in cardiac symptoms when wearing patches. The general advice is not to start smoking. Patches and gums probably deliver nicotine too slowly, often to a sub-optimal level, and nicotine sprays are often unpleasant. Nicotine delivery systems are often used not for smoking cessation but to ward off withdrawal symptoms during periods of enforced abstinence, such as air travel. The APA does not advise acupuncture, the benefits from controlled studies being inconsistent, e.g. Jain (2003) describes it as being no better than sham (not penetrating the skin) acupuncture²⁴⁹⁰.

Advice and continued-rather-than-brief-support given by the GP or practice nurse are effective when combined with nicotine replacement. According to Coleman, (2004b) intensive behavioural support from a trained counsellor is the most effective non-drug intervention, whilst a combination of such counselling and drug treatment is best of all. Twenty percent of those given nicotine replacement therapy with a specialist counsellor’s support will remain non-smokers for one year. Measuring carbon monoxide levels in the breath can test for compliance. The actions of nicotine replacement cannot be explained on the basis of a placebo effect; the effect is dose-related, e.g. 4 mgs is better than 2 mgs. Authorities agree that the higher dose is more effective. Prescribing of smoking cessation products (free in Ireland since April 2001 for medical cardholders - just under 30% of the population) by GPs prior to 2002 was analysed by Tilson *et al.* (2004) Nicotine replacement therapy (NRT) was prescribed for the great majority (47,147 patients, 94.6% - 82.8% patches). 5.4% (2,679) received bupropion. Follow-up during 6 months of a free (2-week) nicotine patch programme in New York City (NYC) found that the highest quit rates were among the foreign born, older people, lighter smokers, and those who received counselling. (Miller *et al.*, 2005) 8.5% of a sample of NYC public high school students admitted to smoking in 2007, down from 17.6% in 2001²⁴⁹¹. NYC uses teenagers to expose retailers who sell tobacco to underage customers. (Anonymous, 2008a)

²⁴⁹⁰ A systematic review (Madsen *et al.*, 2009) questions the analgesic effects of acupuncture.

²⁴⁹¹ 23% and 20% of US and UK adolescents smoked in 2005.

Swedish moist oral snus²⁴⁹² (snuff) might be a healthier option than continuing to smoke tobacco.(Gartner ea, 2007; Britton & Macara, 2008) However, there is a tentative link between snus and pancreatic cancer.(Luo ea, 2007) Also, it is a controversial step to suggest one addictive product to replace another.(Furberg ea, 2008)

Mecamylamine non-competitively blocks ion channels at both central and peripheral nicotinic receptors and reduces the subjective effects of smoking. It can cause constipation, cramps, headache, and dry mouth. There is some evidence that it might be useful in helping people quit smoking if combined with nicotine patches.(Weinberger ea, 2008, p. 430)

Simple intervention by untrained nurses has significantly reduced smoking levels in patients admitted to hospital for coronary artery disease.(Quist-Paulsen & Gallefoss, 2003) Telling patients their spirometric lung age may improve the likelihood of smoking cessation.(Parkes ea, 2008)

Problems in getting people to quit smoking include failure to feel better for a long time and a tendency to weight gain. An abridged version of the motivational approach to interviewing recommended by the Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives (2000) is shown in the box. However, this kind of approach does not always work, even in pregnant smokers.(Tappin ea, 2005)

Young smokers are difficult to help as the evidence base chest is near empty. Youngsters may see no urgency in quitting and services may be viewed as being more geared for their elders; also, cannabis smoking using tobacco as a vehicle is a major obstacle to successful intervention. Therapists are advised to take a supportive, non-confrontational stance.(Grimshaw & Stanton, 2008)

Five 'R's for use with currently unmotivated smokers

Relevance: be specific, e.g. medical risks to self/others

Risks: patient identifies acute (e.g. dyspnoea), long-term (e.g. lung cancer) and environmental (e.g. others take up habit, SIDS) consequences

Rewards: patient identifies positive effects of cessation, e.g. taste of food, improved health

Roadblocks: withdrawal syndrome, weight gain, etc

Repetition: repeat earlier steps at each visit & advise that failure is part of the road to success

One large US company paid employees to stop smoking and to stay off cigarettes with greater success than simply providing information.(Volpp ea, 2009) Longer follow up studies of this type would be revealing.

Prognosis: Two-thirds of smokers express a desire to stop and one-third try to quit the habit each year, only 2% succeeding. At least 80% have returned to smoking within 12 months (Jarvis [2004] puts the number of quits sustained to 12 months at < 3%). Prognostic factors relating to quitting are summarised in the box. About half of all regular smokers die prematurely; stopping to smoke in middle age avoids the bulk of the risk. A Cochrane review found that nicotine substitution treatment increased abstinence up to twofold, but, even with psychotherapy and behavioural therapy, abstinence rates remain very low at 5-15%.(Lancaster ea, 2000) One 8-year follow up of smokers who took part in a randomised controlled trial of nicotine patch therapy found that just under half of the 9% who had stopped smoking for one year had relapsed, leaving 5% of all trial participants continuously abstinent, and relapse rates were similar for patches and placebo!(Yudkin ea, 2003) Counterintuitively, some workers, while reporting high smoking rates among the mentally ill, also suggest that this group may have substantial quit rates. Brief interventions in cardiac inpatients have been shown to help motivated lightly-dependent smokers.(Hajek ea, 2002; West, 2002) According to Molyneux,(2004) only 5% of people who quit smoking successfully continue to use medicinal nicotine regularly.

²⁴⁹² Snus is a moist powdered smokeless tobacco product containing a reduced amount of nitrosamines that is placed under the upper lip for long periods. It is considered a 'white collar' form of tobacco because it does not induce spitting. Boris Yeltsin was a devotee.

Prognosis*(a) For stopping smoking*

Motivation

Living with a significant other person

Hypnotisability

Using transdermal patch: male at least 40 years old

Concern about weight gain

(b) Against quitting

Smoking cannabis

Smoking some cigarettes soon after quitting

Prevention: The best strategy is not to start in the first place. A 10% increase in taxation would cut tobacco consumption by 5-6%. High cost of cigarettes is most effective for the poor, teenagers and females²⁴⁹³. Children should be the prime targets for campaigners; older people respond less to health publicity. Counselling of mothers may reduce passive smoking by children in the home; however, reductions in passive smoking in England since the 1980s is attributable to less smoking parents and not to parents who still smoke not smoking near their children. Advertising²⁴⁹⁴, which has its political protectors, should be banned, as it tends to target women and young people, emphasising the ‘stylishness’ of smoking. Such bans are effective in reducing consumption. Candy cigarettes may increase the chances of young people progressing to tobacco. Voluntary advertising restrictions are insufficient. Tobacco companies allow their advertisements to be seen in movies. Counter-advertising should be financially supported and tobacco company sponsorship of sports should be made illegal. Involving teenagers in an anti-tobacco company poster campaign may be effective in reducing the number of youngsters who smoke. An EU directive banning tobacco advertising was contested by the tobacco industry. The tobacco companies are not beyond bribing politicians in the Third World²⁴⁹⁵. (Sebriè & Glantz, 2006) Nigeria is suing tobacco companies for targeting its youth. (Anonymous, 2008b) The Republic of Ireland banned tobacco advertising and sponsorship from July 2000. England has been much slower than Ireland in this regard, and one Bill suggested that formula one racing should be exempt for four years! (Kmietowicz, 2002) Kawachi (2003) called for an independent nicotine regulatory authority for Britain. The Irish *Public Health (Tobacco) Amendment Act 2004* is monitored by an Office of Tobacco Control. Smoking is banned in public places.²⁴⁹⁶

²⁴⁹³ Packs of 10 cigarette banned in Ireland in 2007 under Tobacco Amendment Acts 2002 and 2004.

²⁴⁹⁴ Advertising of tobacco products will be absent from Irish shops from July 1, 2009.

²⁴⁹⁵ One in 3 smokers live in China. (Wright & Katz, 2007) 70% of men aged 30-60 smoke in China. (Dobson, 2009)

²⁴⁹⁶ Among the provisions are no advertising (in-store/retail), a ban on sponsorship, a ban on smokeless tobacco products (known to cause cancer including mouth and GIT, and heart disease – see below), a restriction on where vending machines can be situated (clubs, bars, hotels – where they must be supervised and activated by a token – tobacco must be stored in a closed container), a ban on confectioneries resembling cigarettes, the use of age cards, powers to get information on and test the composition of products, prohibition of such terms as ‘low tar’ and ‘mild’, extension of smoke-free areas, and the appointment of enforcement officers. Health Boards may take proceedings against persons breaching the provisions of the Act. As of July 1, 2009, anyone who sells tobacco must be registered with the Office of Tobacco Control. There is evidence that legislation for smoke-free workplaces does protect non-smoking bar workers. (Allwright ea, 2005)

The European Parliament voted against a ban on smoking on its premises in 2007. (Spinney, 2007) Norway and Italy introduced similar legislation to the Irish Act although the new Italian health minister was talking of undoing prohibitions on smoking in 2005. (Anonymous, 2005) Scotland introduced its own ban in 2006 with beneficial effects on second-hand smoke exposure. (Akhtar ea, 2007) especially in non-smoking homes. (Haw & Gruer, 2007) The British Health Secretary deferred a limited smoking ban until 2008 in 2004 (Kmietowicz, 2004) and legislation was to spare pubs that do not serve food. (McIntosh, 2005; Woodall ea, 2005) In 2005 the British Health Secretary promised such legislation for 2007, to be reviewed in 2010. In February 2006, the British Parliament voted for a total ban on smoking in public places. In fact, Wales introduced a ban earlier than England in 2007. India banned smoking scenes in new movies in 2005. (Mudur, 2005) The European Court of Justice (Luxembourg) threw out EU legislation against advertising in 2002 insisting that the ban must be directed against items traded across frontiers, forcing Brussels to go through the process afresh. Many authorities have banned smoking in the workplace, public areas, prisons, and restaurants, except in designated areas. In July 2008, the German Constitutional Court upheld the case of small bars that held that because large bars had enough room to divide off areas for smokers the smaller establishments did not have this option, so throwing the German ban into disarray. Smoke-free workplaces protect against passive smoking and encourage smokers to quit or reduce consumption. (Fichtenberg & Glantz, 2002) Even in hospitals, support for smoking bans among staff varies between professionals, e.g. Stubbs ea (2004) found that smokers and nurses in an English psychiatric hospital were more permissive toward smoking on wards than were non-smokers and psychiatrists. A short-

Requirements of a national tobacco control policy are shown in the box.

Components of a national tobacco control policy²⁴⁹⁷

Increase price of and taxes on tobacco at rate above inflation
 Ban all advertising and sponsorship by tobacco industry
 Restrict smoking to designated areas (public places and work sites)
 Reduce passive tobacco exposure, including *in utero*
 Target people at-risk for *starting* to smoke
 “Proof of age” cards required when purchasing tobacco; retailers to be banned from selling tobacco (or worse, e.g. fine/imprisonment) if found selling to minors²⁴⁹⁸
 Education and information, including prominent health warnings (including on packets)²⁴⁹⁹
 Health personnel to provide good example
 Reduce profits of tobacco industry and explore viable economic alternatives
 Monitor trends in use of tobacco and efficacy of interventions
 Very cheap (? on prescription) and accessible nicotine replacement in adequate dosage (current doses may be too low in many cases) and other cessation therapies – all nicotine replacement treatment (NRT) products are free on the British NHS and on the GMS (medical card) in Ireland (but see Yudkin ea, 2003)
 Publish research and disseminate results
 Properly funded national organisation to support and co-ordinate efforts: a tobacco regulatory authority
 Fund policy with revenue from increased price of cigarettes, as in Massachusetts (funding by surtax was withdrawn in California!)
 Prevent smuggling²⁵⁰⁰

Litigation²⁵⁰¹: Increasing numbers of people are winning claims because of the effects of passive smoking, and claims are also being brought because of active smoking, which can succeed even if smoking starts after government warnings are issued.(e.g. Zinn, 2002) One US company (Philip Morris) opened a headquarters far away from US litigation in Switzerland – the same company was found by a federal court to be in violation of civil racketeering laws over a 50-year period (deceit, manipulating cigarette design, and suppressing research) in 2006.(Blum, 2008) The US Supreme Court ruled in December 2008 that smokers could sue the tobacco companies for deceptive advertising practices that suggest that ‘light cigarettes are relatively safe.(Tanne, 2009)

lived ban on public smoking in Helena, Montana seems to reduce morbidity from heart disease.(Sargent ea, 2004) Bans on teenage smoking in the home, in school, and in public places may be effective. In keeping with an EC/EU directive, health warnings were increased in size and details of tar and nicotine yield were added on cigarette packets in the UK in 1992 and health warnings were greatly enlarged in the Republic in 2002. However, despite calls for weaker cigarettes, smokers may compensate for low nicotine yield by puffing more often and deeper, and by smoking more cigarettes. From January 2001 all cigarette packets in Canada carried health warnings that occupy 50% of the front of the pack, although attempts to ban sponsorship of public events by tobacco companies was watered down by the Quebec Court of Appeal in 2005.(Spurgeon, 2005) Following the lead of Canada and Brazil, the EU hoped to follow suit and display such off-putting pictures as rotten teeth and cancerous lungs on packets in 2004 (UK started to do so from October 2008). This would not be a legal requirement. Changing to cigarettes with a lower tar yield may not reduce the chances of myocardial infarction if one continues to smoke. Education about the effects of smoking on the fetus is important. Young Irish children could until recently readily buy cigarettes from retail outlets and retailers are obliged to ensure that prospective customers are at least 18 years of age. However, compliance with such regulations is imperfect.(Mullen, 2009) The Government in England & Wales will increase the minimum age for buying tobacco from 16 to 18 on 1 October 2007. France introduced a total ban in 2008. Some countries allow for designated smoking rooms, e.g. Italy, Sweden, Finland, Iceland, Uganda and South Africa.(Koh ea, 2007) The Netherlands banned smoking in enclosed places in 2007 but closed smoking rooms (where staff may not serve) were allowed; illegal flouting of the legislation continued in cafes at the end of 2008 (Sheldon, 2008) although these cafes removed ashtrays in 2010. Iran and Uruguay have total bans on smoking in public places, Syria following them in 2009.

²⁴⁹⁷ See also Jamrozik (2004a,b), Britton and Edwards (2008), and McKee ea (2009).

²⁴⁹⁸ 23 cases were taken to court in Ireland during 2008 for sales of tobacco to minors resulting in 19 convictions.

²⁴⁹⁹ Australia introduced plain cigarette packets with pictures of diseases in 2010.

²⁵⁰⁰ Price increases following taxation are offset by tobacco smuggling; over 10% of the market share is illicit; and the tobacco industry has been accused of involvement.(Arnott ea, 2008)

²⁵⁰¹ Record individual compensation payments of \$35 bn and \$28 bn (€29 bn, stg. £18 bn) in 2001 and 2002 respectively were handed out in California. The tobacco industry may have deliberately undermined WHO’s anti-smoking efforts by manipulating public opinion. Some American insurance firms owned by tobacco companies have charged smokers almost double for term life insurance! Tobacco companies pressurised companies producing nicotine replacement products to tone down anti-smoking messages. One small US tobacco firm, Liggett, broke ranks, agreeing to settle claims and admitting to the disease-causing and addictive roles of tobacco, in order to get immunity from litigation.

In conclusion, the tobacco industry simply wants to sell their product and has no inherent interest in public health²⁵⁰². It is guilty of undermining the messages of health agencies. Tobacco dependence is a chronic disorder requiring repeated attempts aimed at eventual abstinence. Practical counselling and social support are important ingredients in management, as are sustained-release bupropion hydrochloride (e.g. Zyban) and the various nicotine replacement preparations. At least one of these therapies should be offered to smokers. The present author agrees with Howell (2002) that smoking cessation products should be free to all who wish to stop smoking, not just to those who qualify for medical cards. Doxepin, and probably other antidepressants, have also reduced nicotine craving. Further research is needed to determine the efficacy of pharmacological interventions. Many adult smokers started by buying three cigarettes from shopkeepers whilst underage, a failure of the state to protect them.

Methyl alcohol (methanol)

Mortality from methanol²⁵⁰³ (wood alcohol) poisoning is about 20% because of a metabolic acidosis from toxic metabolites (formaldehyde and formic acid²⁵⁰⁴). It can cause a haemorrhagic encephalopathy. The clinical features include confusion, ataxia, and visceral disturbances. Optic atrophy and cystic necrosis of the putamen may also occur. Treatment strategies include gastric lavage, ethanol or fomepizole (competes for alcohol dehydrogenase so inhibiting formic acid production), folate, bicarbonate, and haemodialysis.

Isopropyl alcohol (isopropanol, rubbing alcohol)

This is found in a number of products, e.g. hair tonic and after-shave lotion. It is converted to acetone, which can be detected in breath (odour), blood and urine. It can cause euphoria, ataxia, dizziness, headache, nausea, vomiting, haematemesis, nystagmus, confusion, coma, hypotension, and respiratory depression. Intoxication lasts about 12 hours. Most cases respond to supportive measures; gastric lavage and haemodialysis are options. Thiamine may be useful.

Ethylene glycol

This is found in antifreeze, windshield washer fluid, and radiator coolants. It is metabolised by alcohol dehydrogenase. A number of poisonous organic acids (e.g. oxalic) are formed. The person appears drunk but does not smell of alcohol. There can be tachycardia, hypertension, pulmonary oedema, metabolic acidosis, hypocalcaemia, myositis, coma, and convulsions. Calcium oxalate crystals form. Without treatment, renal failure often follows. Cranial neuropathies may develop late. Treatment is basically the same as for methanol poisoning: IV ethanol or fomepizole in order to inhibit metabolism. Thiamine and pyridoxine may also help. Severe poisoning is an indication for haemodialysis (which means ethanol or fomepizole dose should be increased) or haemodiafiltration.

Absinthe

This is a green, distilled, highly alcoholic, anise-flavoured spirit derived from herbs (e.g. flowers and leaves of *Artemisia absinthium*²⁵⁰⁵). It fell out of favour in Europe but has made a comeback. It contains the neurotoxin thujone. Opinion varies on its psychoactivity but it has been blamed for such phenomena as delirium and hallucinations. Rizvi et al (2010) have reported a case of acute suicidality that emerged during absinthe consumption.

(Ethyl) alcohol (ethanol)²⁵⁰⁶

'If the storm gets too loud, I take a glass too much to stun myself'. Vincent Van Gogh (1853-1890)

Epidemiology: Not everyone who drinks (ethyl) alcohol²⁵⁰⁷ will develop significant problems from its use. 4% of the global burden of disease is attributable to alcohol, equalling the mortality and morbidity associated with tobacco and hypertension. (Room et al, 2005) Only a quarter of people with alcohol-use disorders seek help, mostly from their GP, and they represent similar numbers in general practice as do hypertensive and diabetic patients. (Schuckit, 2009)

²⁵⁰² In 2007 Philip Morris announced that it would open a research laboratory in the USA. For a discussion on whether and how to collaborate with the tobacco industry see Gray. (2008)

²⁵⁰³ Methanol is present in antifreeze and solvents.

²⁵⁰⁴ Alcoholism is associated with *increased anion gap acidosis* via a number of mechanisms (lactic acidosis, ketosis of starvation, and poisoning with ethylene glycol or methanol). Anion gap = main cations (Na⁺ + K⁺) – anions (Cl⁻ + HCO₃⁻).

²⁵⁰⁵ Also called *Wormwood*. Absinthe is sometimes known as *Green Fairy* due to its colour and is said to have been a favourite of Oscar Wilde.

²⁵⁰⁶ The older term alcoholism is retained here because the author believes in its broad utility. Also, it is a mistake to view alcohol dependence as an all or none phenomenon – it comes in all grades. (Hore, 1991)

²⁵⁰⁷ Ethanol or C₂H₅OH or ETOH.

In 1991 85% of the US population ever used alcohol, 51% being current users at that time. The US National Longitudinal Alcohol Epidemiologic Survey (Grant, 1997) sampled people 18 years or older and found lifetime and past year prevalences of alcohol dependence of 13.3% and 4.4% respectively; males outnumbered females regarding alcohol use and associated disorders. The US National Epidemiologic Survey on Alcohol and Related Conditions²⁵⁰⁸ (Stinson et al., 2005) found a 7.35%²⁵⁰⁹ 12-month prevalence of alcohol use disorders in a representative American sample; co-morbid alcohol and substance use disorders had a prevalence of 1.10%.

Alcohol is the most important deadly ingredient in fatal road-traffic accidents (RTAs: Bellis et al., 2009; Dedford et al., 2009), especially on Saturday nights²⁵¹⁰. The legal age for purchasing alcohol in many US states was reduced to 18 during the late 1970s followed by an increase in RTA deaths. The legal age was raised to 21 in 1984 with the opposite effect. Nearly 50% of the roughly 35,000 annual fatal RTAs in the USA during the early 1990s were alcohol related, someone, usually the driver, being intoxicated, and 5% of drunk drivers killed had already had their licences suspended or revoked! Even aircraft pilots may underestimate the duration of alcohol's effects. (Modell & Mountz, 1990) Impaired psychomotor performance also leads to death from falls, drowning and burns.

Alcohol limits for drivers in the Republic of Ireland, 2009 (from December 1994)

80 mgs/100 mls of blood²⁵¹¹

35 micrograms/100 mls of breath

107 mgs/100 mls of urine²⁵¹²

Alcohol limits for drivers in the Republic of Ireland from September 2011

Road Traffic Bill 2009 passed by Dáil in June 2010

20 mgs/100 mls of blood for learner and professional drivers

50 mg/100 mls of blood for other drivers

European blood alcohol limits for drivers, 2009 (mgs/100 mls of blood)

0.0 Malta, Romania, Slovakia, Czech Republic, Hungary

0.2 Norway, Poland, Sweden

0.3 Russia

0.5 All other countries, including Turkey and North Cyprus

0.8 Luxembourg, Malta, Republic of Ireland (*vide supra*), Switzerland, UK

0.9 South Cyprus

(Germany is 0.3 if involved in an accident, otherwise 0.5)

Other countries, 2009 (examples)

Australia – varies with part of country; Brazil – zero; Canada – 0.8; China – 0.2; Congo – no limit; Egypt – 0.5; India – 0.3; New Zealand – varies with age (< 20 years – 0.3, otherwise – 0.8); Nigeria – zero; Pakistan – alcohol banned; USA – 0.8 (if you are under 21 years and have a level of 0.1 your licence is suspended)

Drivers are less likely to drink if they perceive the risk of detection to be high. Random breath testing increases the perceived risk.

The proportion of a population drinking excessively is largely determined by the average consumption of that population. The latter is determined by price, (Kendell et al., 1983; Purshouse et al., 2010) licensing laws²⁵¹³, and customs and moral beliefs. Islamic countries, especially Saudi Arabia, do not officially allow alcoholic consumption. Jews have low alcoholism rates, even when they live in high-risk districts. People whose jobs carry a high risk of alcoholism include those who have ready access to alcohol (chefs, barmen, brewery workers, kitchen porters - even some laboratory workers), those on expense accounts (salesmen, executives), seamen, printers, vagrants, printers, ex-convicts, doctors, and patients in general. Estimates of

²⁵⁰⁸ This and the National Longitudinal Alcohol Epidemiologic Survey were conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

²⁵⁰⁹ This seems low.

²⁵¹⁰ Cannabis is also associated with fatal road crashes. (Laumon et al., 2005)

²⁵¹¹ This can also be expressed as 80 mg/dL or 17.4 mmol/L.

²⁵¹² Alcohol can be detected in urine for 7-12 hours after the last drink.

²⁵¹³ Although conflict of opinion still exist here.

the proportion of alcoholics among doctors have ranged from 3-15%. Women drink more now than in the past, but this may be improving in England²⁵¹⁴. In England, 38% of men and 23% of women drank more than the upper recommended levels for the heaviest drinking day of the week²⁵¹⁵.(Sengupta & Hoyle, 2005) Average consumption of alcohol in England, Wales and Scotland in 2006 was 13.7, 13.5, and 11.6 units/week respectively.(Creagh, 2008) However, the proportion of men drinking more than 21 units/week fell from 29% to 23% between 2006-2006. A fifth of British adults drank in excess of double the safe limit on their heaviest day of the week in 2007.(Mashta, 2009) Drinking was highest in managerial and professional households, men were heavier drinkers than women, and women were more likely than men to do their drinking at home.

The social stigma associated with the presence of women in pubs has largely disappeared and they have more money to spend. Women are more prone to early cerebral damage despite lower 'peak' alcohol consumption²⁵¹⁶, they may seek help less readily than do men, and they are also more prone to liver damage.

Barriers that may reduce likelihood of women seeking help for substance abuse/dependence

Social stigma

Too busy with offspring or elder care

Fear of loss of children

Fear of drug-using partner

Lack of child care services

Lack of transport

Poverty/lack of health insurance

Perception that drug services are not geared toward women

Heavy, regular drinking occurs at a later age in women than in men but there is a shorter length of time before women develop problems: this 'telescoping' effect in women has been described for other drugs as well as alcohol.(Yates, 2002) 27% of 15-year-olds (29% in girls) in the UK admitted drinking at least 5 consecutive drinks in the previous thirty days (increased from 22% in 1995). Almost half of this alcohol came from their family homes!(Anonymous, 2008d)

Age when drinking began in National Epidemiologic Survey on Alcohol and Related Conditions (Hingson et al., 2006)

Before age 14 years – 47% dependent on alcohol at some point and 13% dependent in prior year

After age 20 years - 9% dependent on alcohol at some point and 2% dependent in prior year

Alcohol costs the Irish economy about €2.6 billion annually. Over 4% of British government revenue derived from alcohol taxes in the mid-1980s during which 750,000 people worked in the British drink trade. The UK government receives about £75 bn annually in excise duties on alcohol. The total annual economic, health and social costs associated with alcohol misuse in England is somewhere between £20-30 bn.(Sengupta & Hoyle, 2005; Hall, 2005; Parker et al., 2008) The US government received \$14 bn annually in revenues from alcohol during the early 1990s. However, the economic cost of alcohol in the US is nearly \$200 bn a year.(Kelly & Renner, 2008, p. 337) About £4m was spent in 1985 by British brewers and distillers on sports sponsorship.

Rates of first admission per 1000,000 for England for both sexes rose from 4 in 1970 to 9 in 1986. The OPCS in Britain gave the following figures for 1993: rate of alcoholism = 4.7% (3M:1F) and rate of drug dependence = 2.2% (2M:1F). Both problems were more prevalent among young adults, especially males aged 16-24 years.

²⁵¹⁴ 17% of women drank more than 14 units/week in 2000, but only 12% did so in 2006.(Creagh, 2008)

²⁵¹⁵ Gilvarry (2006) states that, in the UK, 38% of males and 16% of females aged 16-64 years have alcohol use disorder, and that 21% of males and 9% of females are binge drinkers.

²⁵¹⁶ Women do achieve higher peak alcohol levels than men for the same intake – gastric mucosal alcohol dehydrogenase may be less active in women than in men. Alcohol dissolves better in fat and women have a greater amount of fat and less body water relative men.

Almost 10% of Irish government tax revenue in 1989 came from alcohol. In both Britain and Ireland national alcohol advisory and monitoring groups had to disband because of lack of central support.

Admission to Irish psychiatric facilities for alcohol-related disorders

1991 188.5 per 100,000 of the general population - second only to 'depressive disorders' (235.0): 35%
- 11% of male and female admissions; 5% of inpatients alcohol-related

1992 21% of psychiatric admissions received diagnosis of alcoholic disorder
- Greatest proportion of discharges (46%) within one week of admission.

1993 21% of psychiatric admissions

1994 20%

1999 19% - 44%

2001 18% - 46% of such admissions left within one week*

2002 19% - average length of stay was only 13.8 days

2006 14%

2005 14%

*Admission rate for alcoholism in 2001 was 231.7 and 94.9/100,000 for males and females respectively. Follow up to 2005 confirmed that alcoholic disorders are a common reason for re-admission.(Daly ea, 2007)

The male to female admission ratio for alcohol-related disorders fell from 6:1 in 1968 to 2:1 in 2002.(Walsh & Daly, 2004) Admission rates vary between different services in Ireland,(Okonkwo & O'Shea, 2002) e.g. for 2004 county rates of first admission for alcoholic disorders/100,000 ranged from 68.9 in Co Wicklow to 9.4 in Co Cavan.(Daly ea, 2005)

Ireland had the highest increase in alcohol consumption among EU countries from 1989 to 1999 with an increase in per capita consumption of 41%! Ten other EU countries showed a decrease in consumption.

Alcohol consumption in Ireland²⁵¹⁷

Year	Litres pure alcohol/head of population
1998	11 ²⁵¹⁸
2000	14.2 ²⁵¹⁹
2001	14.3
2006	13.4

Cider consumption increased greatly and a big increase in consumption of spirits was largely a result of 'designer drinks'. About 25% of accident and emergency visits were related in some way to alcohol²⁵²⁰. Hospital-bed days due to alcohol-related disorders in Ireland increased from 55,805 in 1995 to 117,373 in 2004.(Mongan ea, 2007) Public order offences increased by 97% during 1996-2000 again largely related to alcohol.

Ireland topped the European list for binge drinking (> 5 pints or its equivalent/sitting) at 32 binges/year, Britain coming second with 28 binges. Also, Ireland spent more per household on alcohol (> €1,600/household/year) than anyone else in Europe.²⁵²¹ According to the Office of Tobacco Control, Irish 16 and 17 year olds spend €145m on alcohol/year, i.e. €20.09 each/week.(Feely, 2008)

²⁵¹⁷ Figures vary widely wide source. According to Farren (2008) Ireland has the fourth highest alcohol intake in the EU (13.5 L/adult/year) and the highest level of binge drinkers in Europe (34% vs. EU average of 10%).

²⁵¹⁸ Second place in Europe.

²⁵¹⁹ EU average was 9.1 litres of pure alcohol/capita.

²⁵²⁰ This figure was 35% in the UK in a 2003 estimate.

²⁵²¹ In 1999, Ireland spent €1,675/household on alcohol (Denmark next at €531, UK spent €397, and Greece only €146): €1,195 on beer, €248 on spirits, and €232 on wine. According to the CSO, Ireland (Britain in brackets) in 1958 consumed 64.3 L (79.1) of beer and 1.2 L (1.1) of spirit/head of pop.

Alcohol in Ireland (Health Service Executive, 2008)

28% of injuries attending A&E are alcohol-related (A-R) – mainly present midnight to 6 am
 ¾ of these are male; almost ½ are 18-29 year-olds; 13% are alcohol-dependent
 1995-2004: 11,745 discharges for A-R injuries
 1995-2002: 92% increase in A-R discharges
 1994-2003: liver cancer had highest increase in cancer rates (10.7% increase in females and 7.4% in males)
 Unprotected sex: often A-R, especially younger adults (STIs increased by 217% during 1995-2004)
 1990-2006: 7,078 killed on roads, 2,462 being A-R
 1996-2002: public order offences increased by 247% (from 16,384 to 56,822)
 1996-2005: juvenile A-R offenses increased by 438% (from 784 to 4,217)
 1996-2002: 470% increase in public drunkenness
 46% and 42% of homicide perpetrators and victims intoxicated
 44% of respondents to a survey experienced harm by own/other's alcohol use
 63% of women reported alcohol use during pregnancy (of whom 7% drank 6 or more drinks weekly)

A study from Cork (O'Connor *et al.*, 2008) suggests that university students are starting to drink earlier than heretofore and that they have little awareness of safe drinking levels.

The risk of accidental death in Taiwan is significantly associated with alcohol use disorder and with other common psychiatric disorders, especially when the two are combined. (Gau & Cheng, 2004)

Aetiology: Findings related to the aetiology of alcoholism as recorded in the third edition of this textbook are summarised in the box.

Aetiology of alcoholism: early findings and suggestions

Danish adoption studies - increase in alcoholism among the sons of alcoholics

Swedish studies - in some cases transmission is through the male line only but in others it affects both sexes
 Social factors/culture may account for some of the sex differences, e.g. the sex ratio (male: female) is 3:1 in the USA but 1.28 in Korea (Mack *et al.*, 2003); peer-reared female macaques with the 1/s serotonin transporter genotype show a fondness for alcohol, (Barr *et al.*, 2004) an example of an interaction of genes and rearing condition

Learning theory: classical and operant conditioning; modelling, relief of withdrawal symptoms by alcohol acts as a reinforcer for further drinking

Opinion differed on the role of underlying psychiatric problems predisposing to alcoholism – Klerman (1989) found that a substantial proportion of alcoholics had coexistent psychiatric disorders, especially schizophrenia, affective disorder, and dysthymia, other drug abuse, anxiety disorders²⁵²² (especially panic disorder) and PTSD, and he believed that non-medical therapists minimised the extent of psychiatric comorbidity in alcoholics. Kushner *et al.* (1990) felt that alcohol problems in those with agoraphobia and social phobia might be due to drinking alcohol in order to self-treat anxiety, that panic disorder and GAD could arise from excess alcohol intake, but that simple phobia was independent of alcohol. However, not all studies support a relationship between life-long anxiety and alcoholism. (Schuckit & Hesselbrock, 1994)
 P300 amplitude reduction in sons of alcoholics may be genetic²⁵²³ and lead to disinhibition; this phenomenon may be shared with childhood externalising disorders, antisocial personality disorder, and other substance use disorders. In their review of the literature on the P300 in alcoholism, Gamma & Liechti (2002) conclude that a small/reduced P300 amplitude is an endophenotype²⁵²⁴ in children and adolescents marking the risk for alcoholism/other substance abuse/various externalising (and perhaps internalising) disorders. However, they also admit that the similarity of P3 findings in smokers (nicotine) and alcohol-dependent people suggests that 'a substantial part of the P3 amplitude reduction seen in alcoholics or other substance-dependent individuals' might be explained by 'uncontrolled nicotine co-dependence'! Variation in the beta EEG band is highly heritable. Increases in beta power have been noted in alcoholics and their children and have been linked to chromosome 4p (an area containing genes for GABA receptors).

²⁵²² Anxiety may resolve up to 8 weeks after achieving abstinence, the prognosis being worse in those cases that persist. (Chick, 2007, p. 168)

²⁵²³ P3 amplitude appears to be linked to 4q close to the gene for alcohol dehydrogenase.

²⁵²⁴ An endogenous characteristic resulting from the genotype.

Kindling - a concept which has been used to 'explain' a number of conditions, such as alcoholism and relapse in bipolar affective disorder; in the case of experimental animals, a major motor seizure will occur eventually from intermittent electrical stimulation of the brain with a current which was originally insufficient to produce overt behavioural effects; this effect is generated with more ease in the limbic system than in the cortex; it is surmised that it reflects a permanent change in neuronal excitability

Three main models of familial influence on alcohol problems have been suggested: *family disease* model (assumption of roles of alcoholic or co-dependent that perpetuate the problem), *family systems* model (alcohol keeps the family unit together despite consequences), and *behavioural family* model (antecedents and consequences – classical and operant conditioning, and modelling).

Somewhere between 40-60% of the variance in alcohol abuse/dependence is accounted for by genes. There have been proposed linkages of alcoholism to the MNS blood group locus on chromosome 4 and a particular allele of the D2 receptor gene on chromosome 11q, although these reports lack replication and some workers have reported no linkage. Alcoholism, sociopathy and depression may run in families but their interrelationship is complex – there may be a tendency for a greater incidence of the first two diagnoses in males and the last diagnosis in females, although social changes may modify this observation. Hasin and Grant (2002) found that past alcohol dependence increased the current risk of having major depression more than fourfold. Alcoholics have been shown to have a significantly reduced frontal blood flow (largely associated with duration of drinking) which is more marked if there is associated dissociality. Twin and adoption (and combined twin-adoption) studies support an inherited tendency to develop alcoholism in both sexes. (e.g. Kendler ea, 1994) Children of alcohol-dependent parents who are reared by non-alcohol dependent adoptive parents have 3-4 times the risk of developing dependence on alcohol than do adopted children whose biological parents were non-alcoholic. People whose mothers drank when they were in the womb have increased chances of developing alcohol disorders themselves. (Alati ea, 2006) Lappalainen ea (2002) found an increased frequency of the Pro7 allele of a functional neuropeptide Y polymorphism in alcohol-dependent subjects versus controls. The sons of alcoholics have shown abnormalities of the P300 visual evoked response (reduced amplitude and delayed latency), a measure of visual information processing. The exact relationship of the abnormal P3 to alcoholism is controversial, one suggestion being that it actually relates to conduct disorder/antisocial personality disorder. Some people may have a genetic propensity to alcoholic brain damage, possibly related to variants in enzymes involved in B1 metabolism. Alcohol is broken down mainly via the alcohol dehydrogenase/aldehyde dehydrogenase pathway. At relatively high levels of alcohol intake the cytochrome P450 enzyme system becomes involved in the metabolism of alcohol, and this factor may have a role in the development of physiological tolerance.

ALDH2*2 allele (catabolises acetaldehyde more slowly than ALDH2*1) may be a protective factor against alcoholism, but psychological expectation may be more powerful determinants. (Hahn ea, 2006) Variants of GABRA2 on chromosome 4p are associated with the power of beta oscillations in the EEG and to alcohol dependence, or at least to impulse control since they may also be important in conduct disorder and substance abuse.

Animal and human studies suggest that 5-HT uptake inhibition (with, e.g. SSRIs) may reduce craving for alcohol. Smaller amygdala volume in alcohol-dependent subjects appears to be associated with alcohol craving. (Wrase ea, 2008) Early onset alcoholism may be associated with greater serotonergic abnormality and more antisocial behaviour. Alcohol potentiates selective 5-HT₃ receptor-mediated ion currents, an effect blocked by selective 5-HT₃ receptor antagonists like ondansetron. There is some evidence of an effect of ondansetron in reducing alcohol intake in cases with onset before 25 years of age but not in later onset cases. (Johnson ea, 2000) SPECT has revealed reduced brainstem serotonin transporter availability that correlated with lifetime alcohol consumption and with ratings of anxiety and depression during withdrawal. Deficiency of the active mitochondrial form of aldehyde dehydrogenase, common in Orientals, predisposed to a 'flushing response' on ingestion of alcohol. This deficiency, due to a base pair mutation in a single gene, is said to protect against developing alcoholism but, most likely due to cultural changes, binge drinking has increased in Japan and Asians in Hawaii (who possess the variant) have increased their

alcohol intake despite any aversive effects²⁵²⁵. Mission native American Indian adults with alcohol dependence are more likely to have the ADH2*1 allele than the ADH2*3 allele for alcohol dehydrogenase (chromosome 4) compared to those who were not dependent.(Wall ea, 2003) The A1 allele of the D2 receptor on chromosome 12p has been suggested as possibly having some connection with alcoholism, although this finding is hotly contested.

A Boston male twin study (Liu ea, 2004) found substantial genetic influence for age at diagnosis of alcoholism (49%).

Motivation to drink alcohol may be mediated by opioid peptides²⁵²⁶. The reward effect of alcohol could be a result of GABA receptor potentiation (alcohol releases GABA, increases neurosteroid levels, and may increase function of a GABA_A receptor subclass: Krystal ea, 2006). Functional serotonin deficiency is postulated to occur in many addictions.

20-79% of alcoholics have an antisocial personality disorder, compared to 1% of the general population. Alcohol has been described as a 'personality disorder in a bottle'.

Jews uncommonly have alcohol-related problems, which finding most likely relates to custom and moral beliefs. Availability is a major and obvious factor. An increase in the average consumption of alcohol is associated with an increase in the prevalence of heavy drinking and related problems. The drunkenness of children who can buy alcohol-containing sweet drinks is a modern concern. Employment may be a factor, e.g. Walker (1991) reported that women in professional jobs drink more than women in unskilled positions. Judges are said to be at increased risk of dying from alcohol-related diseases.

Cheapness, a relative characteristic, of alcohol is associated with increased consumption.

The modern view is that nature and nurture interact to produce alcoholism. A low-risk environment, such as not experiencing excess alcohol use by the family, may reduce the effect of high genetic loading.(Jacob ea, 2003) Twin studies that search for genetic influences assume that twins share the same environment. There is evidence that twins living together are more likely to be concordant in their normal drinking habits than when they live apart.(Clifford ea, 1984)

Alcohol receptors?

No such receptors have been found

Therefore, does alcohol work by changing membrane fluidity (and thereby alter receptors/channels?)

Acute and chronic alcohol use appears to effect many neurotransmitters (5-HT, opioid, GABA, glutamine) which may mediate reward from alcohol through modulation of dopaminergic neurones in ventral tegmental area and release of dopamine in nucleus accumbens.

Taxonomy: Alcohol abusers tend to remain alcohol abusers and alcohol dependent patients tend to remain alcohol dependent.

The ICD-10 (F10) and DSM-IV classifications are summarised in the table. 'Harmful use' in ICD-10 simply means that one is harming ones health whereas 'dependence' has the same meaning as for heroin.

Alcoholism can be divided into

Alcohol related problems - social, psychological or physical

Alcohol dependence - manifested similarly to any other physical dependence:

Secretiveness

Buying extra rounds

Gulping drinks

Drinking alone

Stocking up

Giving other activities up

²⁵²⁵ People who start smoking often experience disconcerting nausea, cough, and dizziness and yet, if social pressure is strong enough, may persist with the habit to the point of dependence.

²⁵²⁶ Male Rhesus Macaques will consume more alcohol if they carry a particular variant of the mu-opioid receptor gene.(Barr ea, 2007)

Preoccupation with drinking
 Tolerance
 Withdrawal symptoms
 Relief of withdrawals with more alcohol
 High relapse rate
 Loss of subjective feeling of control over drinking behaviour

Jellinek (1960) types of alcoholic

Alpha - drinks to relieve physical or psychological symptoms

Beta - physical complications due to cultural drinking pattern and malnutrition

Gamma - craves for alcohol, loses control of intake, and experiences abstinence symptoms

Delta - no social disruption but continuous intake of alcohol

Epsilon - bout drinking or dipsomania

Cloninger's²⁵²⁷ (1987) two types of familial alcoholism:

Type I - transmitted to men but women can also develop it, drinking starts late, strong gene-environment effect (severity influenced by environment), and loss of control over drinking

Type II - transmitted to men, drinking starts early, less environmental influence and more spontaneous seeking of alcohol, and history of criminality in biological father

Major classifications and alcohol

(a) ICD-10 classification of 'mental and behavioural disorders due to use of alcohol'

Acute intoxication – 7 subheadings

Harmful use²⁵²⁸

Dependence syndrome - 7 subheadings

Withdrawal state – uncomplicated or with convulsions

Withdrawal state with delirium – with/without convulsions

Psychotic disorder – schizophrenia-like, delusional, hallucinatory, polymorphic, depressive, manic, mixed

Amnesic syndrome

Residual and late-onset psychotic disorder* – flashbacks, personality/behaviour disorder, residual affective disorder,

dementia, other persisting cognitive disorder, late-onset psychosis

Other and unspecified groupings

*This classification is a general one for psychoactive substances that may or may not apply to alcohol.

(b) DSM-IV 'alcohol related disorders'

1. Alcohol use – dependence and abuse

2. Alcohol-induced – intoxication, withdrawal (+/- perceptual disturbances), intoxication or withdrawal delirium, persisting dementia, amnesic, psychosis (+/- delusions or hallucinations), mood, anxiety, sexual dysfunction, sleep, & not-otherwise specified

Recognition: Alcoholism (like SLE and syphilis) is one of the great mimics and can present in a myriad of ways and affect any aspect of the alcoholic's or his or her dependants' lives. GPs and non-psychiatric junior hospital doctors may not be good at identifying alcoholics (or asking about alcohol), and psychiatric trainees may be only somewhat at documenting the alcohol consumption of patients but they still often fail to record drinking levels.(Barnaby ea, 2003) We may be ambivalent about our own drinking, ignorant of and complacent towards the effects of excessive drinking, and share the common belief that no one tells the truth about their consumption of alcohol.

The elderly patient is a classic pitfall for missed diagnosis.(McInnes & Powell, 1994; Dunne, 1994; Farragher ea, 1994) Reduced physiological reserve and metabolic efficiency, plus increased volume of distribution (increased fat/muscle ratio) leads to higher blood alcohol levels with greater likelihood of

²⁵²⁷ Babor's Types A and B resemble Cloninger's Types I and II respectively.(Babor ea, 1992)

²⁵²⁸ The difference between *hazardous* use (puts one at risk of harm) and *harmful* use (harm has already occurred) of a substance is contained in the words themselves.

intoxication and harm. Performance impairment, often subtle, is greater in older people than can be accounted for by blood alcohol concentration²⁵²⁹. (O'Connell & Lawlor, 2008, p. 647) A reduced intake does not necessarily mean safe levels, e.g. the elder may reduce his consumption because of decreased tolerance.

Non-intoxication in the presence of a blood alcohol level in excess of 200 mg/dL is pathognomonic of alcoholism. (Wise & Rundell, 2005, p. 157) The Michigan Alcoholism Screening Test (MAST) was devised by Selzer in 1971 (25 weighted questions²⁵³⁰). Pokorny later shortened it to a 10-question test. It is used as a screening test for detecting alcohol-related problems. The *brief MAST Questionnaire* is shown in the box. Mayfield ea (1974) devised the *CAGE Questionnaire* in 1984 (see also Ewing, 1984).²⁵³¹ The *Alcohol Use Disorders Identification Test*²⁵³², (AUDIT; Saunders ea, 1993) a 10-item screening instrument covers alcohol consumption, dependence, and consequences.

Some screening tests for alcoholism

THE BRIEF MAST QUESTIONNAIRE

Circle correct answers*

- | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---------|
| 1. Do you feel you are a normal drinker? | YES (0) | NO (2) |
| 2. Do friends and relations think you are a normal drinker? | YES (0) | NO (2) |
| 3. Have you ever attended a meeting of Alcoholics Anonymous (AA)? | YES (5) | NO (0) |
| 4. Have you ever lost friends/girlfriends/boyfriends because of drinking?
(O) | YES (2) | NO |
| 5. Have you ever got into trouble because of drinking?
(O) | YES (2) | NO |
| 6. Have you ever neglected your obligations, your family, or your work for 2 or more days in a row because you were drinking?
NO (O) | | YES (2) |
| 7. Have you ever had delirium tremens (DTs), severe shaking, heard voices or seen things that were not there after heavy drinking?
YES (2) NO (O) | | |
| 8. Have you ever gone to anyone for help about your drinking? | YES (2) | NO (0) |
| 9. Have you ever been in hospital because of drinking? | YES (5) | NO (0) |
| 10. Have you ever been arrested for drunk driving or driving after drink? | YES (2) | NO (0) |

*The numbers in parentheses are the scores for each response. A score of 6 or more is registered as POSITIVE. The scores are not shown to the user in the form in which the questionnaire is used in practice, but they are given here for convenience sake.

THE CAGE QUESTIONNAIRE

Have you ever felt you should cut down on your drinking?

Have people ever annoyed you by criticising your drinking?

Have you ever felt bad or guilty about your drinking?

Have you ever had a drink first thing in the morning (eye-opener) to steady your nerves or to get rid of a hangover?

The cut-off point for alcoholism is between 2 and 3.

Each affirmative answer gets a score of 1. The maximum score is 4. A score of 2 or more is suggestive of alcoholism.

One unit of alcohol equals a half-pint glass of beer, lager or stout, a glass of wine or sherry, or a single measure of spirits.

1 unit of alcohol

8-9 G (sources vary) of (absolute) alcohol (a measure of convenience)

Increases blood alcohol by approximately 15-20 mg/dl

The amount that is metabolised in 1 hour

²⁵²⁹ Physical and cognitive status and concurrent medication contribute.

²⁵³⁰ Scoring of MAST: 0-4 no alcoholism; 5-6 possible alcoholism; > 6 probable alcoholism. Versions for geriatric use include G-MAST and brief G-MAST.

²⁵³¹ The CAGE has high specificity but only modest sensitivity. (Sackett, 1996, pp. 15-21) A negative CAGE does not rule out alcohol misuse.

²⁵³² Score of 8 or more in AUDIT = harmful/hazardous drinking; at least 13 in females and 15 in males = dependence. The *Drug Use Disorder Identification Test* (DUDIT, Stuart ea, 2003), modelled on the AUDIT, is an eleven-item self-report measure that screens for substance-related problems (other than alcohol). AUDIT can be useful in screening for problematic drinking histories in patients attending general hospitals because of self-harm. (Holdsworth ea, 2010)

Heavy drinking is not synonymous with physical dependence on alcohol.

Alcoholism is a major problem in industry and identification is based on unacceptable behaviour, impaired performance, lateness, 'inexplicable' accidents, and excessive absenteeism. Having excess drink on each occasion of drinking (say > 5 drinks) is as important as the overall intake when it comes to social and personal complications. (Room ea, 1995) This is the classic Irish pattern. The 'Monday morning syndrome' is too well known to require further description here. Between 8 and 14 million working days were lost through drinking in the UK in 1985, and absenteeism through alcohol misuse was estimated (Anonymous, 1989) to cost about stg £700m a year. The annual cost of alcohol misuse in Britain for 1990 was estimated at stg £2 bn if one includes ill health, crime, accidents and absenteeism. The direct annual specialist treatment costs in 1990 in the US and UK respectively was \$10.5 bn and stg £400m. Treatment of illnesses and injuries due to alcohol costs the British Government in the early twenty-first century up to £176 bn annually, total costs (absenteeism, crime, etc) reaching as high as £20

bn. (www.number10.gov.uk/files/pdf/interim-report.pdf) Barry (2003) gives the healthcare costs related to alcohol for the Republic of Ireland in 1999 as €279,000,000 and the total cost to society at €2,366,000,000. This takes no account of the effects on health, relationships, and child development.

About 25% of acute male admissions to medical wards, and an even higher percentage in the case of acute surgical emergency admissions, are related to alcohol misuse.

A number of tests are suggestive of excessive alcohol intake. Although not fully accepted (having low specificity for alcohol and often abnormal in ill non-alcoholics), the following tests are suggestive of alcoholism: A raised serum gamma glutamyl transpeptidase (GGT or γ GT) reflects heavy alcohol consumption during the preceding weeks²⁵³³. A raised mean corpuscular volume (MCV), a toxic effect on erythropoiesis, reflects long-term drinking habits but is not particularly sensitive or specific²⁵³⁴. A raised GGT due to alcohol to about half the index level after about three weeks of abstinence whereas a raised MCV takes longer to normalise and will therefore not help in relapse detection. Carbohydrate-deficient transferrin (CDT) is an alternative marker of excessive alcohol ingestion and may be more accurate than GGT for drinking during the previous fortnight. (Conigrave ea, 2002) Liver disease does not lead to raised CDT unless it is severe²⁵³⁵. Perhaps these tests are more useful if measured in series rather than acutely. If someone looks sober with a high blood alcohol level this suggests a regular heavy alcohol intake - the levels can still be high 24 hours after the drinking has stopped²⁵³⁶.

Reasons for misdiagnosis of excess alcohol consumption in the elderly (O'Connell ea, 2003)

Non-disclosure

Low index of clinical suspicion

Low referral rate because seen as understandable (poor health and life changes) and untreatable

Atypical (falls, confusion, depression) or masked (comorbid physical or psychiatric disorders) presentation

Non-applicability of 'sensible limits' (metabolic changes, ill health, increased sensitivity to alcohol)

Lack of consequences (social, legal, occupational)

Focus on recent (rather than lifetime) intake by diagnostic criteria and screening instruments

Self-disclosure of alcohol intake by elderly Irish interviewed in their homes showed a significant positive association between consumption and being male and widowed. (Greene ea, 2003)

Psychiatric problems: Deliberate self-harm is associated with alcoholic disinhibition. It was held that 6-20% of alcoholics committed suicide, although the accepted figure has dropped below the lower of these two figures in recent years²⁵³⁷. The alcoholic who was seen as at the highest risk for suicide was older, socially isolated, male, had made previous suicide attempts of serious intent, was physically ill and had a

²⁵³³ Gamma glutamyl transpeptidase levels are also elevated with hepatic disease, obesity, and a number of drugs (e.g. anticonvulsants, statins, and antidepressants, particularly lofepramine). Serum aspartate amino-transferase (AST) has lower sensitivity for alcohol than does GGT.

²⁵³⁴ MCV is raised macrocytic anaemia, hypothyroidism, hepatic disease, and anticonvulsant drugs.

²⁵³⁵ However, few laboratories measure CDT.

²⁵³⁶ This fact is well known to the authorities who may catch drivers on the way to work the morning after a night of drinking.

²⁵³⁷ Farren (2008) points out that low mood before drinking may be greatly exacerbated by alcohol. He also believes that 25% of suicides are solely due to alcohol (alcohol is present in the bodies of 58% of Irish suicides).

poor work record, and had recently lost a close relationship through death or separation. Elder abuse is usually related to chronic stress and low support, but a minority is associated with drug and alcohol abuse, sociopathy, intellectual disability, and various psychiatric disorders in the abuser, e.g. schizophrenia. (e.g. Wrigley, 1991)

Depression in alcohol misusers is often secondary to alcohol, although it may be primary in some cases (bipolar > unipolar depression). Opinion differs on how long a period of sobriety is required before an (alcohol-) independent diagnosis of depression can be made. A period of 2 weeks is often quoted. Certainly, alcohol use greatly complicates the management of depression. (Salloum ea, 2000) Disulfiram can precipitate depression. Tricyclic antidepressants may cause cardiotoxicity in combination with alcohol or in overdose (Anonymous, 2008c) and SSRIs are safer.

Alcoholics are at high risk for marital breakdown, unemployment, accidents, doing physical or psychological harm to others, becoming involved in unwise sexual encounters, and of imprisonment. Alcohol is a common cause of depression. It may also causes gradual coarsening of the personality and the emergency of sociopathic traits.

Syndromes associated with alcohol

Alcoholic dementia: Lishman (1987) suggested that this condition might account for at least 10% of all end-stage dementias. Intellectual function should be tested after a period of total abstinence. Exclude continued inebriation and control for the effects of general neglect. Radiological studies revealed decreases in brain volume in many chronic alcoholics. This is at least partially and very slowly reversible with prolonged abstinence: it is debated as to whether reversal is due to rehydration of the brain or repair of neurones or myelin. (Mann ea, 1993) Autopsies of alcoholics revealed a significant decrease in cortical neurone numbers in superior frontal cortex with no difference from controls in terms of number of neurones in motor cortex. In both cortical areas there was evidence that alcoholics had smaller, shrunken neurones than controls.

Possible causes of cognitive disorders in alcoholics include premorbid intellectual deficit, direct ethanol neurotoxicity, neurological complications of alcohol (e.g. Korsakoff's), thiamine or nicotinic acid deficiency, recurrent head trauma, and hepatocerebral degeneration. There is controversial evidence that light to moderate drinking may reduce the chances of developing dementia, even when other variables like smoking are controlled for. (Ruitenberga, 2002; Stampfer ea, 2005; Fratiglioni ea, 2008, p. 395) More common than dementia is subtle cognitive dysfunction that may interfere with understanding of medical advice and adherence to a plan of treatment.

Alcoholic hallucinosis: This state may follow immediately from DTs or may commence whilst still drinking. Most cases clear up quickly after drinking is stopped although hallucinations may return if drinking restarts. The auditory hallucinations occur in the presence of a clear sensorium and may take the form of 'noises'²⁵³⁸, conspiratorial and threatening whispering, accusatory voices, etc. The patient may become paranoid, hostile or suicidal as a result, or he/she may take flight or hide. A few cases may have schizophrenia (5.3%, 11.5%, and 19% in Bendetti [1952], Victor & Hope [1958], and Cutting [1978]) – such cases are more likely to have a family history of schizophrenia and poorer premorbid adjustment. Treatment includes detoxification from alcohol and neuroleptics for hallucinations. The therapist may try to stop neuroleptics after a few months. ECT may sometimes be required.

*Delirium tremens*²⁵³⁹ (*Rats, DTs, alcohol withdrawal delirium* in DSM-IV): This occurs in less than 5% of cases in alcohol withdrawal. (American Psychiatric Association, 2002, p. 300) Often occurs when alcohol intake is stopped, such as following hospitalisation. Usually starts at night. It lasts from 2-7 days (sometimes weeks in the elderly – may resemble dementia). Features include intense fear, restlessness, illusions, delusions, visual hallucinations²⁵⁴⁰, tremulousness, ataxia, vestibular dysfunction²⁵⁴¹, hypertension, tachycardia, leucocytosis, impaired hepatic function, and pyrexia. An interesting phenomenon which may occur during the DTs is the carrying out of occupationally related activities, e.g.

²⁵³⁸ One patient of the author heard 'crashing glass' that he interpreted as deliberately meant to be upsetting.

²⁵³⁹ Term coined by the English physician Thomas Sutton (1767-1835) in 1813. The DTs is sometimes known as Saunders-Sutton syndrome. William Saunders (1743-1817) was a Scottish physician.

²⁵⁴⁰ E.g. little animals (microzoopsia).

²⁵⁴¹ The patient feels the floor is moving or that he is rising as if in a lift (elevator).

the barman who 'pulls pints' for the other patients with the bars of his cot (*occupational delirium* or *professional delusions*). Fever may be part of the core syndrome or due to a complication such as aspiration pneumonia. High blood pressure, tachycardia, and tremor may be obscured by medication that the patient is taking, e.g. calcium channel blockers, beta-blockers, and alpha-2-adrenergic agonist drugs. The mortality rate from DTs has fallen due to better detection and medical management, decreasing over the years from 20% to c. 1%. Treatment involves sedation (e.g. alprazolam or chlordiazepoxide in large doses²⁵⁴²), thiamine, folate, multivitamins, a high-carbohydrate diet, and the reversal of metabolic disorders. Haloperidol may be needed for psychotic agitation. Infection requires attention. Death can be due to cardiovascular collapse, infection, and self-injury²⁵⁴³ when restless. If pneumonia²⁵⁴⁴ occurs the death rate can climb to 25%. Subdural haematoma, pneumonia, and meningitis should be considered in the disorientated alcoholic. The dosage of drugs should be tailed off to zero over a number of days. The cumulative effects of sedatives may cause hypostatic pneumonia if they are prescribed in high dosage for too long, especially with an IV infusion of chlormethiazole (Heminevrin) which may also cause death from respiratory depression²⁵⁴⁵. Ethanol could potentially be used to treat the DTs and is less cumulative than Heminevrin: 30 mls initially, followed by 10 mls every hour in 50% dextrose. Fluids should be replaced sparingly because alcoholics have a reduced ability to excrete water and a tendency to cerebral oedema.

Black-outs: This refers to memory lapses ('memory blackouts') following a heavy bout of drinking despite observers not noting any significant change in level of consciousness. (It therefore differs from amnesia secondary to gross impairment of consciousness due to very high levels of alcohol.) It can occur in normal drinkers. It is more likely to be abnormal if it occurs frequently or if the episodes of amnesia last for days. The drinker cannot remember where he left his car, who was with him at the time, and so on. Interestingly, people may find their way home unaided and not remember doing so. State dependent phenomena may sometimes occur, e.g. he can only complete a letter or remember at which hotel he left the car when intoxicated again. It should be noted that blackouts can be caused by BZDs, especially those of high potency like triazolam. (Greenblatt ea, 1991)

Pathological (idiosyncratic) intoxication (manie à potu): This has been used as a defence in courts and refers to the occurrence of extreme intoxication despite the intake of a relatively small amount of alcohol. Many experts doubt its existence. It is not included in DSM-IV or ICD-10.

Hypoglycaemia: Factors responsible include malnourishment (low hepatic stores of glycogen) and inhibition of hepatic gluconeogenesis by alcohol. Care should be taken because it is possible to induce Wernicke's encephalopathy by injudicious replacement of glucose in a thiamine (B1)-deficient patient. Ethanol-induced hypoglycaemia does not respond to glucagon. Treatment is with glucose **and** vitamin B1. Children who take alcohol (not necessarily in large quantity), binge drinkers, and chronic alcoholics have relatively little glycogen reserve in their livers and may present in a comatose state with hypothermia.

Fever: This may occur during alcohol withdrawal. Causes are hypovolaemia, lung (incl. aspiration and TB)/meningeal/peritoneal (esp. with ascites – ideal culture medium – bacterial peritonitis can occur in the absence of abdominal pain/tenderness or leucocytosis)/urinary tract (incl. catheter-related) infection, alcoholic hepatitis²⁵⁴⁶, and acute²⁵⁴⁷ and chronic²⁵⁴⁸ pancreatitis. Consider CSF examination in confused patients.

Hypertension: About a quarter of alcoholics have systemic hypertension, often resolving (to various degrees) with abstinence. Always consider excess alcohol intake in hypertension that is poorly controlled.

Retrolbulbar neuritis and optic atrophy: These are classically associated with methanol but can occur with ethanol. The retrolbulbar neuritis usually comes on insidiously and causes central loss of vision, typically red-green blindness.

²⁵⁴² Use lorazepam if there is very poor liver function. Propofol may be effective when everything else fails.

²⁵⁴³ These patients put themselves at risk and may fall from a height or otherwise injure themselves.

²⁵⁴⁴ Pneumonia in the alcoholic may be caused by unusual pathogens, e.g. anaerobes and gram-negative organisms such as *Klebsiella pneumoniae*. (Moss & Burnham, 2006)

²⁵⁴⁵ Clomethiazole with alcohol is very likely to depress breathing.

²⁵⁴⁶ The cardinal pointer is rapid onset of jaundice +/- pyrexia, ascites, proximal muscle loss, and, in severe cases, encephalopathy. The liver is usually big and tender. (Lucey ea, 2009)

²⁵⁴⁷ Gallstones, alcohol, endoscopic retrograde cholangio-pancreatography (ERCP), and idiopathic cases account for 9 out of 10 cases of acute pancreatitis.

²⁵⁴⁸ 8 out of 10 cases in the West are accounted for by alcohol misuse.

Epilepsy: Many alcoholics experience convulsions. There are many causes. Focal CT abnormalities are unlikely if there are no focal neurological abnormalities and if the answer is in the affirmative to 50% or more of CAGE items. When they form part of a withdrawal state they may be referred to as 'rum fits' (can occur from day 1-14 after cessation or diminution of alcohol intake). Other causes, such as a subdural haematoma, should be considered.

Neuropathy: This is usually a polyneuropathy, with sensory, motor and autonomic signs: numbness, paraesthesiae, burning dysesthesia, pain, weakness, muscle cramps, gait ataxia, loss of tendon reflexes (including ankle jerks), defective perception of touch and vibration sensation. Autonomic disturbance is less common and may carry an increased risk of death. Sensory disturbance takes on a glove-and-stocking distribution. Treatment: if the patient stops drinking and if nutrition is improved the prognosis should be good.

Myopathy: This is more common than one would think from the number of cases diagnosed in clinical practice. There are a variety of possible causes, such as a direct toxic effect of alcohol or hypokalaemia. It can be acute and necrotizing, or have a more insidious onset. The acute form may occur during an alcoholic binge, when the patient develops weakness, tenderness, and swelling of the affected musculature. He may develop dysphagia and congestive heart failure. There may be elevated CPK levels and myoglobinuria. The chronic form is more common and pain is less prominent - there are muscle weakness and atrophy, especially affecting the hip and shoulder girdles.

*Liver disease*²⁵⁴⁹: A steady daily intake of alcohol is more hazardous to the liver (cirrhosis) than is intermittent drinking. Cirrhosis usually occurs with an intake greater than 40 G in men and 20 G in women. The person has been drinking at such levels for at least 5 years (usually > 10 years) before developing cirrhosis. It is interesting that some chronic heavy drinkers do not develop cirrhosis.

Foetal alcohol syndrome: This is described elsewhere.

Marchiafava-Bignami disease: This uncommon condition, described in 1903, is often diagnosed at postmortem. It affects chronic alcoholics who develop symmetrical degeneration of myelin in the central part of the corpus callosum. The cerebellar peduncles may also be involved. Neurological features include ataxia, hemiparesis, dysarthria, aphasia, apraxia, coma, and grand mal seizures. Most cases have psychiatric manifestations, e.g. personality change, confusion, mania, paranoid states, various delusions, depression or dementia. There are 3 possible courses: early coma with fatal outcome, prolonged survival in a demented state, and, rarely, recovery. Lesions can be seen on CT or MRI: necrosis of corpus callosum and the adjacent subcortical white matter.

Cerebellar degeneration: This is due to degeneration of Purkinje cells in the cerebellar cortex, possibly because of thiamine deficiency. The patient has usually been drinking for many years. (Moderate longterm alcohol intake causes Purkinje cell loss before any macroscopic atrophy appears.) It may have an insidious or an abrupt onset. Gait ataxia (broad-based gait) and dysarthria occur. Nystagmus is rare. Treatment involves stopping drinking and taking thiamine. The patient may then stabilise or improve.

Central pontine myelinolysis (osmotic demyelination syndrome): This rare disorder of cerebral white matter (Adams ea, 1959) has many causes. Rapid correction of hyponatraemia (common in beer drinkers, esp. when replacing vomited fluids with hypotonic fluids) may be a factor in the aetiology (although not invariably so: Ibrahim & Hennessy, 2007), the condition presenting a day to a week later. This hyperosmolality may affect brain water levels. The patient is usually an alcoholic but alternatively he may suffer from non-alcoholic hepatic disease (including Wilson's disease), hyperemesis gravidarum, malnutrition, burns, cancer, Addison's disease, anorexia, or hyponatraemia due to diuretics. It is a rare complication of liver transplantation. (Surman & Prager, 2004, p. 664) There is a triangular area of pallor at the base of the pons. There are demyelinated axons with preserved cell bodies and (not always) cavities in the centre of the lesions. The patient may have paraparesis, quadriparesis, dysarthria, dysphagia, inability to protrude his tongue, various tendon reflex changes, the presence of Babinski's sign, abnormal conjugate eye movements, and the 'locked-in' syndrome (normal consciousness, paralysed, can communicate with eyes and eyelids). MRI scans are especially useful in advanced cases for showing up the lesions. High-resolution CT can also detect the lesion during life.

²⁵⁴⁹ Discharges for alcohol-related liver disease in Ireland rose by 147% in the period 1995-2004.

Ischaemic strokes in young males were reported in association with alcohol during the 1980/90s in the US, Sweden and Scotland.

The Amnestic syndrome (ICD-10) or disorder (DSM-IV): Wernicke and Korsakov²⁵⁵⁰ described their patients in 1881 and 1889 respectively. Wernicke (of 'receptive dysphasia' fame) described an acute neuropsychiatric reaction to severe vitamin B1 deficiency with nystagmus, abducens and conjugate gaze palsies²⁵⁵¹, gait ataxia, and global confusion. (Most cases of Wernicke's encephalopathy present with delirium alone²⁵⁵²: Harper ea, 1986) All of Korsakoff's cases had polyneuritis and so he called it 'psychosis polyneuritica'. The lesion is usually in the posterior hypothalamus and nearby midline structures. Less commonly there are bilateral hippocampal lesions (in this type there is less tendency to confabulate – confabulation and loss of insight into memory loss may be most marked in thiamine-deficiency cases). Wernicke's encephalopathy is best seen as the acute end of a spectrum with Korsakov's (or Korsakoff's) psychosis (or syndrome) at the chronic end, i.e. the Wernicke-Korsakov syndrome. The core of the chronic condition is an inability to form new memories with or without confabulation²⁵⁵³. One can usually demonstrate that certain forms of memory capacity are retained, e.g. those not requiring a verbal component like visuospatial and geographical memory: the classic example is the inpatient that has no problem negotiating his way to and from the pub! There may be a hereditary susceptibility related to genetic polymorphism for the transketolase enzyme that requires thiamine as a co-factor²⁵⁵⁴. (Blass & Gibson, 1977) The causes of the syndrome are alcohol, hunger strikes, the life of a prisoner-of-war, anorexia nervosa, thyrotoxicosis, GIT ulcers and cancers, intestinal obstruction, vomiting (hyperemesis gravidarum), haemodialysis, post-encephalitis (e.g. Herpes simplex), puerperal sepsis, anoxia (e.g. CO poisoning), vascular lesions (e.g. infarction of the thalamus, subarachnoid haemorrhage) and gastric/bariatric surgery (Foster ea, 2005). The mechanism in alcoholism, malnutrition and malabsorption is thought to be thiamine deficiency. Other causes are bilateral temporal lobectomy, tuberculous meningitis, and tumours of the third ventricle. In cases with slowly expanding brain tumours, the amnesia will be progressive. Wernicke's encephalopathy may be precipitated by alcohol withdrawal and perhaps by the first meal. **One should never give glucose IV to an alcoholic without first making sure that he has enough thiamine** (e.g. Pabrinex, a parenteral multivitamin preparation) **because Wernicke's encephalopathy may be precipitated**. Jackson and Teece (2004) found oral thiamine as effective as parenteral thiamine in the emergency department. It is often stated that it is pointless giving in excess of 50 mgs of thiamine daily because the body cannot absorb any more than that. However, absorption is often poor in alcoholics, and the present author gives at least three times this dose. (*Poor response to thiamine may indicate hypomagnesaemia, which responds to magnesium sulphate.*)

In the famous Victor ea (1971) study of 245 patients with the acute Wernicke-Korsakov syndrome (most of whom were chronic alcoholics) 17% died early on, all except 4% developed Wernicke's encephalopathy, and 84% of those followed up developed a typical amnesic syndrome. Once the condition became established, 50% never got better, 25% had a partial recovery, and only 25% had a complete recovery. In practice, there is no point in expecting the full clinical picture to be seen in life. Harper ea (1986), in a necropsy study, found that 80% of patients with the Wernicke-Korsakov syndrome were not given this diagnosis during life. Only a small percentage had classical signs. Therefore, it is essential to have a high index of suspicion in 'at risk' groups, especially alcoholics. Investigation of thiamine status may be helpful, and if the diagnosis is suspected, parenteral thiamine should be given. The EEG may be relatively normal or show diffuse slowing CT scans in Korsakoff's psychosis. Korsakoff's psychosis may show areas of reduced density in the dorsomedial thalamus and MRI in Wernicke's encephalopathy has shown hyperintense areas surrounding the third ventricle and aqueduct.

Sexual dysfunction: Alcohol is directly toxic to the testis causing a reduction in germ cells, a reduced area of the seminiferous tubules, injury to Leydig cells, reduced plasma levels of testosterone, testicular atrophy, impotence and diminished libido.

Enterocyte dysfunction: Damage to subcellular organelles can cause folate deficiency and steatorrhoea.

²⁵⁵⁰ Variable spelling in the literature.

²⁵⁵¹ In practice, ocular disturbance affects only a **minority** of cases.

²⁵⁵² The suddenly ataxic, confused patient may be mistakenly diagnosed as simply drunk!

²⁵⁵³ Patients are often uninterested in their lack of past memories. There may also be perseveration (stuck in the one groove).

²⁵⁵⁴ Reduced red cell transketolase is a marker of thiamine deficiency.

The offspring of alcoholic parents are at increased risk for phobic and anxiety disorders, antisocial symptoms, and abuse of alcohol and other substances.

Physical problems: The severity of intoxication at a given alcohol concentration is typically greater when the concentration is rising than when it is falling²⁵⁵⁵. This possibly reflects the occurrence of acute tolerance to alcohol during a single episode of drinking. Smoking slows gastric emptying and thereby delays alcohol absorption.

Sudden death is not uncommon in the alcoholic population, e.g. from myocardial infarction, epilepsy, pneumonia or accidents. Death certificates rarely mention alcohol. Anderson (1988) estimated that there were 28,000 deaths each year in England and Wales associated with alcohol consumption in people aged 15-74 years. In a study of Swedish conscripts aged 18-19 years, Andreasson ea (1988) found that a high alcohol consumption (more than 250 G/week) carried a 2.1 times greater chance of dying over 15 years than did a moderate consumption (1-100g./week). 36% of all deaths were due to violence, suicide or probable suicide.

In a prospective study at an Irish general hospital, Maguire (1988) looked at the relationship between alcohol and acute hospital admissions. Of 197 consecutive admissions, 19.3% were alcohol-related. 15% were positive on screening for alcohol, 17% of all patients admitted were heavy drinkers and were mainly males. 42% of road-traffic accidents and 67% of overdoses were alcohol-related. Alcohol problems and alcohol-related cognitive impairment were found, retrospectively, to contribute significantly to the difficult-to-discharge group of acute patients in Cork.(Popoola ea, 2008) Another study from Cork (Bradshaw ea, 2008) found that alcohol use disorders were common among general hospital admissions and are often undetected or documented in case notes.

Some physical problems in alcoholics

Fatty infiltration of liver, hepatitis²⁵⁵⁶

Cirrhosis²⁵⁵⁷, hepatoma, oesophageal varices

Zieve's syndrome²⁵⁵⁸

*Hepatorenal syndrome*²⁵⁵⁹

Gastritis, peptic ulcer, haematemesis, and pancreatitis²⁵⁶⁰

Anaemia, macrocytosis, thrombocytopaenia, platelet inhibition

Smoking-relating cancers²⁵⁶¹

Osteoporosis

Proximal myopathy +/- myositis

Cardiomyopathy

Atrial fibrillation (holiday heart syndrome)²⁵⁶²

Increased effect of other drugs

Fetal alcohol syndrome

Various infections²⁵⁶³, including TB

Gout²⁵⁶⁴

²⁵⁵⁵ 'Mellanby effect'.

²⁵⁵⁶ In *alcoholic fatty liver*, a reversible condition if the patient abstains, fatty acids are not oxidised and triglyceride production increases. There are usually no symptoms but abdominal pain, nausea and vomiting may occur. Alcoholic hepatitis, associated with cell death, inflammation and a disproportionate rise in AST (relative to ALT), can be fatal. Right-sided abdominal pain, fever, icterus, ascites and, sometimes, encephalopathy, may be present.

²⁵⁵⁷ In cirrhosis there is loss of hepatocytes and fibrosis with the outlook being poor if the patient continues to drink.

²⁵⁵⁸ The rare association of alcoholic hepatitis consisting of transient hyperlipidaemia, icterus, and haemolytic anaemia.

²⁵⁵⁹ This consists of acute renal insufficiency due to severe liver dysfunction. There may be hypotension, hypertonic urine, low urinary output, low urinary sodium, and indicators of advanced liver disease. The kidneys are normal and the cause may be vasoconstrictive. Pre-renal uraemia from other causes needs to be considered.

²⁵⁶⁰ *Acute pancreatitis* carries a 10-40% mortality rate. Chronic pancreatitis leads to pancreatic insufficiency, malabsorption, and chronic pain with the possibility of analgesic dependence.

²⁵⁶¹ Controlling for smoking, wine may be less likely to cause oropharyngeal and oesophageal cancer than is beer or spirits.

²⁵⁶² This may occur despite having a normal heart during excessive intake of alcohol or whilst withdrawing from alcohol.

²⁵⁶³ Chronic alcoholics are at increased risk of post-operative infection. This may be related to immune suppression.(Spies ea, 2002)

Alcohol depresses granulocyte function so that one may see a case of serious systemic infection and a low or normal white cell count.

²⁵⁶⁴ According to Choi ea (2004) who studied men, alcohol is strongly associated with an increased risk for gout. Beer confers a greater risk than spirits and moderate wine intake does not increase the risk.

Relatively low alcohol intake may have a protective effect on the heart, (e.g. Jackson ea, 1991; Mukamal ea, 2003) although the margin between what is safe and what is harmful is narrow (Doll ea, 1994b; Fuchs ea, 1995; Bobak ea, 2000) and the evidence for any protection is not certain. (Hart ea, 1999) Also, the role of alcohol in protecting the heart may vary with the sex of the patient²⁵⁶⁶. (Tolstrup ea, 2006) This alleged protective effect may be due to increases in the levels of HDL₂ and HDL₃, subfractions of high-density lipoprotein cholesterol²⁵⁶⁷. However, indiscriminate advice to non-drinkers to take up alcohol for health reasons is extremely inappropriate. Alcohol may reduce the chances of starting a pregnancy. (Jensen ea, 1998)

Metabolic problems associated with alcoholism include hypoglycaemia (fasting or reactive), ketoacidosis, hyperuricaemia, hypomagnesaemia, hypertriglyceridaemia, and hypercortisolaemia with non-suppression on the DST²⁵⁶⁸. Moderate intake of alcohol in healthy people may increase insulin sensitivity and possibly reduce the risk of non-insulin dependent diabetes.

Fatal residential fires can arise from many sources (living in a mobile home, no fire detector, etc), but alcohol abuse is one of the commoner causes.

Causes of death include cirrhosis, cancer²⁵⁶⁹ (mouth, pharynx, larynx, liver, breast cancer in women), injuries, etc. Smoking approximately doubles the mortality risk. Official alcohol-related deaths for the Republic of Ireland for 1990, 1995 and 1999 were 106, 146 and 269 respectively.²⁵⁷⁰

Acute effects of alcohol may involve disruption of glutamatergic neurotransmission by inhibition of the response of the NMDA receptor. Prolonged inhibition of NMDA receptors might then lead to supersensitivity (up-regulation) of these receptors. Schumann ea (2008) reported that variations in the NMDA NR2A subunit are associated with positive family history, early onset alcoholism, maximum number of drinks in adults, and risky adolescent drinking habits.

Alcohol and TCAs have a 3-phase relationship. During acute alcohol intake TCA first-pass metabolism is blocked leading to up to trebling of TCA plasma levels. During medium term alcohol intake CYP enzymes are induced causing lowering of TCA levels. Finally, during chronic alcohol ingestion there is a fall in hepatic CYP enzyme concentration and reduced liver mass and possibly portacaval shunting with increased TCA plasma levels.

Alcohol withdrawal symptoms may be due to a reduced inhibitory function²⁵⁷¹ and/or increased activity of excitatory systems²⁵⁷². Nevertheless, CSF GABA levels do not appear to differ between abstinent alcoholics and normal controls or between alcoholics with or without a history of withdrawal seizures. If a person drinks heavily at a single sitting they may experience hangover²⁵⁷³ effects. They may also experience mild withdrawal symptoms: insomnia, restlessness and increased REM sleep. Rarely, transient, generalised choreoathetoid movements may occur during alcohol withdrawal.

Alcohol withdrawal (Ling ea, 2003)

Uncomplicated

Starts hours after stopping alcohol, lasts 1-2 days: tremor, headache, irritability, some autonomic overactivity, photophobia

²⁵⁶⁵ Kelly ea (1971) showed that high-potency IV vitamins B and C could reduce the subjective effects of alcohol intoxication. Michael Kelly (personal communication, 1978) used IV vitamins as an aide to distinguish decreased levels of consciousness due to alcohol from that due to head injury, the former being responsive (more alert) but not the latter. Apart from cranial trauma, **alcoholic coma** (excess alcohol alone or alcohol-induced hypoglycaemia) must be differentiated from other pathology, e.g. lung or meningeal infection, bleeding from the GIT, or liver failure. Rarely there may be a need for IV fructose or peritoneal dialysis to speed up the decline in blood ethanol concentration.

²⁵⁶⁶ The Tolstrup ea (2006) from Denmark looked at men and women aged 50-65 years. Women were protected by drinking more and men by drinking more often!

²⁵⁶⁷ Alcohol also inhibits thromboxane and platelet aggregation as well as enhancing thrombolysis.

²⁵⁶⁸ Can also develop a pseudo-Cushing's syndrome.

²⁵⁶⁹ Acetaldehyde is known to be carcinogenic. (Proschl & Seitz, 2004).

²⁵⁷⁰ These seem on the conservative side since alcohol misuse is said to contribute to as many as 22,000 deaths each year in England. (Sengupta & Hoyle, 2005)

²⁵⁷¹ Reduced GABA activity or decreased activity of the α -2 adrenoreceptor.

²⁵⁷² Potentiation of NMDA by depletion of magnesium or overactivity of the catecholaminergic system and CRF.

²⁵⁷³ Various factors contribute to this, e.g. dehydration (meningeal stretching?) and acetaldehyde.

Complicated**[1]**

- (a) similar to uncomplicated but with anxiety, increased reflexes, transient hallucinations, and greater autonomic disturbance
- (b) alcoholic hallucinosis
- (c) seizures
- (d) DTs

[2]

Protracted withdrawal syndrome (PWS) -lasts weeks-years and may not be unique to alcohol, e.g. opiate (hypotension, hyperalgesia, low tolerance for stress), BZD or cocaine (craving) users may report similar experiences
 Most common features of PSW: EEG changes, irregular anxiety/muscular tension, tremor, depression, breathing/pulse/blood pressure, sleep problems, fatigue, and poor short-term memory. PWS may carry greater risk of relapse.

Acute management: Detoxification is with a benzodiazepine in reducing doses, e.g. chlordiazepoxide or alprazolam for the average patient or lorazepam if there is significant hepatic insufficiency. Anticonvulsants such as carbamazepine (e.g. 800 mg/day) can be used instead of BZDs, but there is nothing to be gained from combining the two.(Lingford-Hughes ea, 2004) Vitamins are replaced and physical complications are sought and treated. Preparations containing multivitamins are available for oral and parenteral use – thiamine can be injected on its own or in a multivitamin preparation such as Pabrinex. Anaphylaxis has been described in association with parenteral vitamin (IV > IM) injections. Beta-blocking drugs such as propranolol have been used to reduce the risk of arrhythmias and to manage prominent tachycardia and tremor. Should a neuroleptic be required it is better to use haloperidol because it is less like to cause seizures and is safer than many other agents in the presence of liver disease. Most patients with mild-to-moderate withdrawal symptoms do not require in-patient detoxification, but can be treated safely and effectively as outpatients, with considerable cost savings.(McCollam ea, 1992; Okonkwo & O’Shea, 2002) Inpatient treatment should be considered for patients with serious medical illness, a history of serious withdrawal symptoms or seizures, mental state changes, or marked autonomic lability.

Longterm management: Vaillant (1999) states that ‘In alcoholism, as in much of medicine, we dress the wound; we do not heal it’.

The idea of rejecting a patient for a liver transplant because of a history of excess alcohol intake *per se* is ethically flawed.(Masterton, 2000)

Disulfiram (Antabuse) or calcium carbimide²⁵⁷⁴ cause nasty symptoms if taken before alcohol by increasing production of acetaldehyde. (See later)

Aversion therapy is rarely used today because of associated ethical problems and low effectiveness.

Disulfiram was once commonly used in aversion therapy (alcohol given at the same time). Other agents that were used for this purpose were emetine and apomorphine.

Alcoholics Anonymous (AA)²⁵⁷⁵, with Al Anon for relatives and partners, ACOA for ‘adult children of alcoholics’ and Al-Ateen for the teenage children of alcoholics. (Synanon is an American organisation for drug addicts). AA gives immediate help to people from other members, it insists on total abstinence, it holds regular meetings, and it does not appeal to all cases. The alcoholic must confess his problems to the group. Sponsorship of one AA member by another AA member offers help during a crisis. Some alcoholics like AA, others do not. Some object to references to God or a ‘Higher Power’. There is some degree of self-selection in AA attendance, and while there is some evidence that it may not be more efficacious than other interventions (Walsh ea, 1991) the general consensus is that it helps many alcoholics. Problems for research include anonymity among attendees and a stated prohibition on engagement in research.

The *Minnesota Model*²⁵⁷⁶, commonly used in the US, dates to the 1950s and conceptualises alcoholism in biopsychosocial and spiritual terms to be treated holistically in a variety of settings by multi-professional

²⁵⁷⁴ No longer available.

²⁵⁷⁵ Founded in Akron, Ohio in 1935 by Dr Bob S (Robert Smith), 1879-1950, and Bill W (Wilson), 1895-1971. The first European meeting was held in Dublin in 1946. The *Big Book of Alcoholics Anonymous* is a form of bibliotherapy. Bibliotherapeutic approaches to alcoholism are somewhat superior to doing nothing at all but may not be as efficacious as more extensive interventions – the best results seem to be for those cases who seek treatment (**not** severe cases) and offer specific strategies such as setting goals or showing how one can cope without resorting to drinking.(Patton ea, 2008, p. 315)

²⁵⁷⁶ Dan Anderson PhD (1921-2003, psychologist from Minneapolis) and Nelson Bradley MD (Canadian, medical superintendent) witnessed institutionalised alcoholics at Willmar State Psychiatric Hospital, Minnesota and decided to attend AA meetings to see what they could learn from them. They became interested in two programs based on the philosophy of AA: Pioneer House (founded 1948 to treat alcoholics with families) and Hazelden (founded 1949 to treat professionals). The 12-Step approach was manualised in 1992:

teams with abstinence as the goal. The Twelve Steps of AA are seen as essential. Motivational enhancement and CBT strategies (to tackle unhelpful thinking - 'stinkin' thinkin'') are used. It is generally recognised as being effective. (Project MATCH Research Group, 1998)

Certain centres use specialised techniques, e.g. Glasser's reality therapy, (Glasser, 1965) a confrontational technique. CBT, social behaviour and network therapy, (UKATT Research Team, 2005a,b) and motivational enhancement²⁵⁷⁷ are other techniques used. Longer duration in treatment correlates with better outcome but, since this does not hold up with random assignment to different lengths in therapy, the relationship is probably biased by better-motivated clients choosing to stay in treatment for longer. (APA, 2002, p. 294)

Various attempts have been made to teach alcoholics to control their drinking, e.g. showing him a film of himself when drunk, teaching him to stop gulping drinks and how to identify stimuli to drinking and to find alternative ways of dealing with them. It is as yet very difficult to predict who can control their drinking. Buspirone²⁵⁷⁸ (5-HT_{1A} agonist) and SSRIs seem to reduce craving for alcohol. (O'Shea, 2000)

The RCPsych recommended a 10-point code to help people drink sensibly:

- Don't drink every day of the week (a 2-3 day break gives the body a chance to recover)
- Don't use alcohol to treat emotional problems
- Don't drink alone
- Don't use alcohol as a hypnotic because tolerance causes a rapid onset of the tendency to increase the amount consumed
- Don't drink alcohol whilst taking other drugs
- Don't drink alcohol on an empty stomach (food delays the absorption of alcohol)
- Try to introduce a non-alcoholic drink during sessions
- Sip drinks (do not gulp)
- Pace yourself (aim to be the slowest drinker in company)
- Always dilute spirits.

According to the RCPsych (1979) if you drink half a bottle of spirits or 8 pints of beer per day you are at high risk for dependence²⁵⁷⁹. The College proposed so-called 'safe levels', e.g. 4 bottles of beer per day, 4 doubles of spirits or one bottle (standard size) of wine. Increases in the number of units considered to be safe as suggested by the British government in 1995 met with deserved criticism! The relationship between dose of alcohol consumed and mortality may be stronger for young people. (White ea, 2002)

Employee health programmes wherein alcohol-related problems are monitored and detected cases are directed to treatment agencies are important. However, alcohol problems reappear before work problems do and close monitoring is advisable for at least a year after resumption of work.

Opinion on whether controlled drinking is possible for some alcoholics is still divided, (Tobin ea, 1993) although most programmes advise total abstinence. It is extremely difficult to foretell which problematic drinkers can control their alcohol intake in advance.

Pharmacotherapy

Drug therapy should form part of a package that aims to improve psychosocial outcome.

Verapamil delays the elimination of alcohol with prolonged feeling of intoxication, which may prove dangerous when driving. The hepatotoxic effect of paracetamol is increased in chronic heavy drinkers because the production of its hepatotoxic metabolite is increased and its metabolism is diminished. Binge drinking whilst taking metformin increases the risk for lactic acidosis.

Disulfiram: Work done in Copenhagen in 1940s showed that diethylthiuram disulphide ingestion caused certain symptoms if even small amounts of alcohol were taken subsequently. (O'Shea, 2000) Efficacy

'Twelve-Step Facilitation'. This led to Project MATCH, a randomised, controlled, multi-site study. The Minnesota Model has spread internationally.

²⁵⁷⁷ In *motivational enhancement therapy* (individual or group), designed to help people who seek help, the therapist creates an atmosphere of respect and adopts a non-judgemental/non-confrontational stance. The client is asked to use his own skills and resources for change, the responsibility being his. Resistance is met by a change in tactics. A meta-analysis (Burke ea, 2003) suggested that this approach is helpful in reducing alcohol consumption, at least in the short term.

²⁵⁷⁸ Buspar was withdrawn, December 2009.

²⁵⁷⁹ Lower levels should not necessarily be viewed as safe.

largely depends on fear of a reaction. It is ineffective if not taken: supervision by a responsible adult helps to ensure effectiveness. The recipient feels hot in the face, develops intense flushing, the scleral vessels become dilated and there are palpitations, dyspnoea, nausea and headache. The reaction tends to abate in a few hours and the patient is left feeling sleepy. After he has oxidised the alcohol he feels well again. Disulfiram interferes with the excretion of acetaldehyde (irreversible binding with ALDH), an intermediary product in the oxidation of ethyl alcohol. A severe reaction is treated with vitamin C 1Gram and an antihistamine such as mepyramine maleate IV.

The oral solution of the protease inhibitor amprenavir contains propylene glycol which is metabolised by aldehyde dehydrogenase; if the latter enzyme is inhibited by disulfiram the patient may develop propylene glycol poisoning. Therefore, do not give amprenavir and disulfiram to the same patient.

Side effects of disulfiram include fatigue, skin disorders²⁵⁸⁰, impotence, a metallic or garlic taste and hepatotoxicity. Opinion differs on the potential for liver damage, some authors suggesting regular LFTs. Disulfiram²⁵⁸¹ can cause delirium or a psychosis in clear consciousness, probably by increasing mesolimbic DA via inhibition of dopamine beta-hydroxylase. This includes a tendency to exacerbate schizophrenia²⁵⁸². One criticism of using disulfiram²⁵⁸³ is that the dose given is too low. Giving the patient an experience of an 'antabuse effect' before discharge from hospital is much less popular (and of questionable ethics) than heretofore. Disulfiram is a good crutch for those who are motivated.²⁵⁸⁴ Neuropathy (including optic neuritis) from disulfiram is rare in low doses; it usually takes several months to come on and it usually clears up if the drug is stopped early. Fatal liver reactions are rare (1/25,000 treated/year). A combination of isoniazid and disulfiram can cause ataxia. Delirium may result when disulfiram and an MAOI (e.g. isocarboxazid) are co-administered. Disulfiram inhibits CYP2E1 oxidase which, potentially, could lead to toxicity from diazepam (not lorazepam), TCAs, carbamazepine, phenytoin, or warfarin. Disulfiram metabolites inhibit P450 3A4 and so can lead to toxicity from immunosuppressant drugs. (Cornelius ea, 2003)

Other causes of antabuse reactions

- Metronidazole (Flagyl)
- Carbimide²⁵⁸⁵
- Pargyline²⁵⁸⁶
- Coprine²⁵⁸⁷
- Cephmandole (parenteral cephalosporin)
- Procarbazine²⁵⁸⁸
- Oral ketoconazole
- Griseofulvin (rare)
- Paraldehyde
- Chloramphenicol
- Percutaneous absorption of monosulfiram (Tetmosol - anti-scabetic agent)
- Chlorpropamide (Diabinese – a sulphonylurea that reduces blood glucose levels), some people experience marked facial flushing if they take alcohol (blocked by naloxone and reproduced by an enkephalin analogue with opiate-activity - this response might be inherited as a dominant trait along with diabetes mellitus)

²⁵⁸⁰ Disulfiram mobilises stored nickel which may lead to 'recall' dermatitis in people who are allergic to nickel.

²⁵⁸¹ Or rather its diethylthiocarbamate metabolite.

²⁵⁸² Use only low doses in schizophrenic patients.

²⁵⁸³ This author often prescribes one tablet of 400 mg three times a week.

²⁵⁸⁴ This author has certainly seen alcoholics who drink on regardless!

²⁵⁸⁵ *Citrated calcium carbimide* was introduced in the 1950s and it gives a milder reaction than disulfiram with alcohol. However it was subsequently withdrawn from the marketplace. Carbimide reversibly inhibits aldehyde-NAD-oxidoreductase and it does not inhibit dopamine-beta-hydroxylase.

²⁵⁸⁶ Antihypertensive agent.

²⁵⁸⁷ Coprine or coprin is found in the Common Ink Cap mushroom *Coprinus atramentarius*. Coprine inhibits acetaldehyde dehydrogenase.

²⁵⁸⁸ Cancer chemotherapy agent and weak MAOI.

- Paraldehyde – not to be given with disulfiram as latter blocks paraldehyde metabolism with formation of acetaldehyde

Surgical implants of disulfiram have been tried but they have been largely abandoned because of evidence of a lack of both pharmacological and clinical effects due to insufficient blood levels. Improvements in assessing compliance by testing for metabolic products of disulfiram are possible. One could test for diethylamine in the urine and carbon disulphide in the breath.

Alcohol comes in many guises, including certain vitamin preparations and cosmetics.

Chlormethiazole (Heminevrin): This is a hypnotic, anxiolytic and anticonvulsant and is derived from the thiazole moiety of thiamine. The pharmacology is not clear, apart from GABA enhancement. It has a short half-life of 6-8 hours. Alcohol increases the bioavailability of chlormethiazole; it possibly impairs its normally extensive first pass hepatic metabolism. Barbiturates and chlormethiazole have additive effects. Chlormethiazole potentiates phenothiazines and butyrophenones. In cirrhosis there is a tenfold increase in the bioavailability of chlormethiazole. Cross-dependence is common. Chlormethiazole can cause nasal tingling, rhinorrhoea, conjunctival irritation and GIT upset. It has been given by infusion for toxæmia of pregnancy and status epilepticus. Too much fluid load (IV) can cause hyponatraemia. It is toxic in overdose, causing deep coma and a centrally mediated respiratory depression. This author prefers chlordiazepoxide or alprazolam when detoxifying alcoholics. In its former distinctive colour chlormethiazole was known 'on the streets' as 'duck eggs'.

SSRIs: There is controversial evidence that SSRIs may reduce craving for alcohol²⁵⁸⁹. High doses (e.g. fluoxetine 60 mg daily) may or may not moderately reduce alcohol consumption.(Lingford-Hughes, 2002) 5-HT2 blockers like ritanserin have not been helpful.

*Acamprosate*²⁵⁹⁰ (*Campral EC*), which reduces craving for alcohol²⁵⁹¹, seems to stimulate GABAergic neurotransmission and inhibit excitatory amino acids like glutamate. Acamprosate suppresses elevated c-fos expression it has been shown to inhibit calcium channel upregulation in rodents withdrawing from alcohol. The aversive effects of ethanol withdrawal coincide with a reduction in dopaminergic activity in the mesolimbic system and an increase in the release of glutamate in the nucleus accumbens; there is also increased expression of brain c-fos, an immediate-early gene. It should be started just after detoxification.(Lingford-Hughes, 2002) Like other such treatments, at least some form of counselling should accompany its prescription. Dosage is 2 (333 mg/tab) tablets 3 times a day if the patient is more than 60 Kg in weight²⁵⁹². Food reduces its availability. In fact, the drug is poorly absorbed from the GIT and several days are required before useful blood levels are reached. It is secreted in urine and breast milk and is not significantly metabolised. It is not bound to serum proteins. One year of treatment post-detoxification is recommended, longer if the patient relapses. It does not interact with alcohol. Treatment should continue despite lapses/relapse. It is not advised to prescribe it to children or the elderly. It should be avoided if the serum creatinine is over 120 micromol/L, if there is severe liver failure²⁵⁹³, if the patient is pregnant (teratogenic in rats), or during breastfeeding. Side effects include diarrhoea, nausea, vomiting, bloating, abdominal pain, pruritus, various rashes, and, probably at the placebo rate, fluctuations in libido. Bismuth relieves GIT symptoms, but the dose may need to be reduced for severe or persistent problems. Overdose may lead to hypercalcaemia. The calcium in acamprosate may inactivate tetracyclines. Acamprosate may be combined with disulfiram (Lingford-Hughes, 2002) or naltrexone.(Kiefer ea, 2003) *Naltrexone (Revia, Nalorex)*, previously used for the management of heroin dependence, was first used to treat alcohol dependence in the US. Animal work suggested that naltrexone would reduce craving for alcohol. Naltrexone competitively binds with opiate receptors and antagonises the actions of exogenous opioids. The theory is that alcohol is reinforced by the action of endogenous opioids: transgenic mice lacking beta-endorphin reduce voluntary alcohol consumption relative to normal (wild-type) mice²⁵⁹⁴. The

²⁵⁸⁹ According to Farren (2008) SSRIs are not helpful in non-depressed alcoholics overall, and fluoxetine may worsen early-onset alcoholism whereas sertraline may ameliorate late-onset alcoholism.

²⁵⁹⁰ Calcium bis-acetyl homotaurinate. It resembles GABA structurally.

²⁵⁹¹ This was first noticed in animals.

²⁵⁹² 2 tabs mane + 1 tabs midday + 1 tab nocte for lighter patients.

²⁵⁹³ Childs-Pugh classification C.

²⁵⁹⁴ People with a particular mu opioid receptor polymorphism may respond better to naltrexone.(Farren, 2008)

blockade of endorphin activity when alcohol is imbibed results in attenuated dopamine release from the nucleus accumbens. It can cause nausea (usually mild and transient) in some patients. Liver toxicity can occur with high doses of naltrexone²⁵⁹⁵. 80-90% is extracted and metabolised in the liver²⁵⁹⁶. The half-life is 10 hours²⁵⁹⁷. There is a low terminal elimination phase half-life (96 hours). If there is any likelihood of opioid use/dependence then a naloxone²⁵⁹⁸ (Narcan) challenge²⁵⁹⁹ must be carried out unless it can be confirmed that the patient has been opioid free for the previous 7-14 (some say longer) days. Attempts to overcome blockade by taking huge doses of opioids can threaten life. Medical need for opioids may require larger doses than usual, with the danger of respiratory depression. Side effects include nausea, vomiting, diarrhoea, constipation, fatigue, nervousness, irritability, anxiety, somnolence, headache, dizziness, poor appetite, disturbed sleep, abdominal pain or cramps, increased or decreased energy, joint and muscle pain, thirst, nasal drip, low mood, rash, delayed ejaculation, reduced potency, and chills. Not all research agrees that naltrexone is effective (Krystal ea, 2001) and there have been reports of depression and suicide associated with it.(Lingford-Hughes, 2002)

Injectable naltrexone (Vivitrol) is available in the US. Once-monthly injections improve compliance. Problems arise if the patient needs analgesia²⁶⁰⁰.

Tiapride, a non-addictive substituted benzamide, has effects of DA receptors. It reduces withdrawal symptoms and promotes abstinence, and is said to have anxiolytic and antidepressant properties.

Topiramate, a sulphamate fructopyranose, may inhibit mesocorticolimbic DA release by increasing GABA and reducing glutamate activity respectively. There is some evidence that it assists people to remain abstinent (Johnson ea, 2003, 2004, 2007; Swift, 2003), although evidence tends to be based on short-duration study and use of self-reports.

Ondansetron, a 5-HT₃ antagonist, reduces DA release in the mesocorticolimbic system. It reduces alcohol consumption in rats and may be of some benefit in humans²⁶⁰¹.

Pabrinex: This is a high potency mix of vitamins B and C. It comes as IM (7 ml) and IV (10 ml) preparations, each containing 2 ampoules²⁶⁰² that are drawn up into a syringe to mix them just before use. It can cause hypotension and mild paraesthesiae. If mild allergic reactions are experienced (sneezing or mild asthma) it should not be used again. Repeated injections of preparations containing high concentrations of vitamin B1 can cause anaphylaxis, which should be anticipated.

Baclofen (Lioresal, Baclopar): This GABA-B receptor agonist, a voluntary muscle relaxant, may reduce craving for alcohol.(Addolorato ea, 2007)

Others: Acupuncture, ACE inhibitors, DA agonists (bromocriptine, lisuride), and thyroid hormones have had their advocates. BZDs should generally be avoided longterm in persons prone to alcohol abuse or dependence, but there is a small group of patients where their use may 'maximize abstinence and minimize morbidity from alcohol'.(Lingford-Hughes, 2002, p. 557)

Prevention: The outlook is that of a chronic, relapsing disorder. Cross dependency with other drugs is common. Prevention is difficult. The price of alcohol could be raised. In 1990, the Irish spent more on alcohol than their government spent on the health services! In British Columbia advertising was banned but the TV and radio from the US carried the advertisements across the border. The USSR had a big problem with alcoholism and no advertisements, although relaxation of controls in the Russian Federation saw a worsening of the problem²⁶⁰³. Alcohol (and tobacco) is a major contributor to premature mortality in Russian males.(Leon ea, 2007; Zaridze ea, 2009) A 2004 English Cabinet report (Cabinet Office, Prime Minister's Strategy Unit, 2004) does little to reduce harm caused by alcohol and leaves too much to the goodwill of the drinks industry. Controlling the hours of opening of bars and cutting down on off-licence sales gives equivocal results. Health education is desirable but the results are hard to measure. US states

²⁵⁹⁵ Check LFTs at baseline and at intervals.

²⁵⁹⁶ First pass metabolism.

²⁵⁹⁷ Sustained release depot naltrexone is under development.

²⁵⁹⁸ Causes briefer withdrawals than naltrexone.

²⁵⁹⁹ 0.2 mg Narcan IV – if no adverse reaction at 30 seconds give 0.6 mg IV and observe for 30 minutes for withdrawals.

²⁶⁰⁰ Try a non-opioid first. If opioids are needed they may need to be given in larger doses and more often than usual.

²⁶⁰¹ Especially in early-onset alcoholism.(Farren, 2008)

²⁶⁰² 5+5 ml for IV, 5+2 ml for IM.

²⁶⁰³ Intriguingly, the upper house of Russia's parliament struck down a bill outlawing public drinking in 2004! The Duma (lower house) allowed a lobbyist from the tobacco industry to have 'light' included in cigarette advertisements in 2008!

that raised the legal drinking age to 21 had less suicide in their 18-20 year olds.(Birckmayer & Hemenway, 1999)

Prohibition in the USA during 1920-33 was not sustainable and may have been at least partly responsible for the so-called 'Capone Era'.

In a twelve-month follow up of two groups of alcoholics, one given various and intensive interventions and therapy and the other given advice only, the outcome was the same on several parameters.(Edwards ea, 1977) Similar findings were reported from a meta-analysis of 20 controlled studies.(Moyer ea, 2002) Evidence for the effectiveness of brief interventions (e.g. confrontation, advice, counselling, information) for problem drinking in a general hospital remains controversial.(Emmen ea, 2004) Also, the few trials that have followed up patients for long enough suggest that the effects of brief interventions do not last beyond a year.

Vaillant (1996) followed up two groups of alcohol dependent patients: by age 60, 18% and 28% of college students and inner-city dwellers respectively were dead, 11% of the former and 30% of the latter groups were abstinent, relapse was less likely if sobriety was maintained for five years, and a return to controlled drinking was uncommon.

Gilder ea (2008) assessed 580 American Indians. 254 had DSM-III-R alcohol dependence. The rate of remission was 59%. Remission was associated with female sex, married status, earlier onset, and self-reported alcohol-linked depression. Non-remission was associated with drinking despite knowledge of associated medical problems and self-reported alcohol-linked anxiety.

The main factors contributing to relapse are negative or positive emotional states, social influences, conflict with others, and the urge/temptation to take a drink.

1988 RCPsych consensus recommendations re alcohol

Overall reduction in consumption

Increase price²⁶⁰⁴

Reduce advertising

Increase licensing hours

Random breath testing²⁶⁰⁵ of drivers

Reduce permissible levels of blood alcohol for drivers²⁶⁰⁶

Men to drink no more than 21 units/week

Women to drink less than 14 units/week²⁶⁰⁷

Government should fund campaigns against alcoholic misuse

Beverages should be clearly labelled with strength and amount of alcohol contained in them

Alcohol education for medical students and doctors

Medical profession to lead by example

Available/adequate/early help for every problem drinker

Help for the families of problem drinkers

Increase research funding

2008 British Medical Association (BMA, 2008) alcohol control recommendations

Reduce access – control hours of sale and outlet density; increase taxes (proportional to alcohol content; outpace inflation)

Enforce licensing laws - no sale if underage; cut out sale of drinks like 'alcopops'²⁶⁰⁸

Reduce drink driving – reduce legal limit from 80 to 50 mg/100ml; random testing of drivers

Education and health promotion – put guidelines on labels

Early intervention and treatment – routine screening and brief intervention to decrease hazardous drinking; expand specialist services for excess drinkers

²⁶⁰⁴ Perhaps less tax on low- or non-alcoholic drinks.(Hall, 2005) Alcohol was 54% more affordable in the UK in 2003 than in 1980.(Gilmore & Sheron, 2007)

²⁶⁰⁵ Breathalyser test for alcohol invented by Martin Wright, National Institute for Medical Research, London, UK, 1967.

²⁶⁰⁶ Especially for the first two years of driving.

²⁶⁰⁷ The pregnant woman should either not drink at all or only now and again.

²⁶⁰⁸ Flavoured alcoholic drinks aimed at youth.

Despite increasing evidence of the damage caused by alcohol, neither the government nor the public appear to want to do very much about it. Dunbar *et al.* (1987) suggested random breath testing and a zero limit for learner and first year drivers because they are more likely to have accidents even with low levels of alcohol in their blood. Prevention strategies can be divided into primary²⁶⁰⁹ and secondary²⁶¹⁰. According to Room *et al.*, (2005) increasing taxation on alcohol,²⁶¹¹ reducing its availability, and measures against drinking-and-driving are effective policies. They stress that ‘population-based approaches have been neglected in favour of approaches oriented to the individual that tend to be more palliative than preventative’.

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²⁶⁰⁹ Price rises, reduced availability, education, use of alternative drinks and leisure pursuits.

²⁶¹⁰ This refers to early identification and treatment.

²⁶¹¹ The start of 2010 saw a fall in the price of alcohol!(McAuliffe, 2010)

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21

Neuropsychiatry

Brian O'Shea

'What man can know the intentions of God? Who can divine the will of the Lord? The reasonings of mortals are unsure and our intentions unstable; for a perishable body presses down the soul, and this tent of clay weighs down the teeming mind'. (Book of Wisdom, 9:13-14)

'Mental health professionals continue to employ a mind-brain dichotomy when reasoning about clinical cases'. (Miresco & Kirmayer, 2006)

'It's an open question whether the human brain, with its ineffable complexity, is capable of understanding itself'. (Dew, 2009)

This section covers heterogeneous disorders which may present with, or be complicated by mental symptoms, there existing however a known or suspected organic aetiology.²⁶¹² The uninformed may jump to a false diagnosis of psychogenic disorder when the unexpected occurs, e.g. in the case of *geste antagoniste* (tricks patients discover to overcome neurological problems) as when a patient with dystonia can run but not walk or can walk in reverse but not forwards; the patient with spasmodic torticollis (cervical dystonia) may be able to control the spasm by pressing on the ipsilateral or contralateral chin; or the person who ameliorates blepharospasm by singing or pressing on the lateral canthus. On the other hand, psychogenic disorders, if continued for long enough, may produce secondary somatic effects (e.g. abnormal posture that persists during sleep).

Links between neurological and psychiatric disorders may arise in different ways

Neurological insult may produce focal disorders like frontal lobe syndrome or generalised conditions like dementia and, most likely, schizophrenia

Depression, anxiety or conversion disorder may arise, e.g. as a reaction to neurological disorder

Neurological disorder may exacerbate personality traits

Personality disorder may present as neurological disease, as in factitious disorder

Cost

McHugh et al (2007) reported on cost of 'disorders of the brain' (DOB) in Ireland. The most relevant groupings are shown in the table. Costs (€ at 2004 prices) per inhabitant of DOB were €227 (direct healthcare), €116 (direct non-medical) and €443 (indirect), with a grand total of €775. Mood disorders were the most costly DOB. 'Intangible' costs (suffering, quality of life²⁶¹³, etc) were not calculated. For comparison, total costs (in €) for migraine, epilepsy, CVA, MS, Parkinson's disease, and cerebral tumour were 64, 37, 35, 17, 12, and 9 respectively. DOBs consume 3% of GNP and two-thirds of this is accounted for by "raditional" psychiatric disorders (€2.035 bn out of €3.049 bn).

²⁶¹² Placing a disorder or syndrome or symptom in this section is largely a matter of convenience and should not be construed as meaning that other disorders have no biological basis. DSM-IV has dropped the term 'organic' to avoid the probably mistaken assumption that 'functional' disorders do not have an organic component.

²⁶¹³ *Quality of Life in Alzheimer's Disease Scale* (QoL-AD; Logsdon et al, 1999), for completion by carers or patients, has 13 items including physical/mental health, relationships, finance, and an overall evaluation. It can be used with all degrees of dementia. To get the best view of quality of life one should seek the views of as many people as possible. Staff are influenced by behaviour/dependency and patients may be anxious or depressed.

Costs/inhabitant of certain disorders in Ireland (€) (McHugh ea, 2007)				
Disorder	Direct healthcare	Direct non-medical	Indirect	Total
Mood	56	0	195	251
Addiction	33	7	89	129
Anxiety	47	0	46	93
Dementia	13	66	0	79
Psychoses	38	7	0	45

The cost of dementia to the UK economy is £17 bn (€24 bn) (Strachan ea, 2008; Burns & Iliffe, 2009a) and carers save UK tax payers £6 bn annually. (Butler, 2008) Ireland has only one neurologist per 202,000 of the population.

Cerebral anoxia

This may be acute (restlessness and anxiety, clouding of consciousness, and poor concentration proceeding to coma and death or to memory difficulties, dementia and temporal lobe epilepsy) or chronic (personality change and cognitive deficits). (cf. carbon monoxide poisoning below)

Four types of anoxia/hypoxia

Anoxic anoxia - insufficient O₂ reaches blood, e.g. not enough O₂ present in breathed air

Anaemic anoxia - low blood haemoglobin level or O₂ is displaced by another gas such as CO

Hypoxia - may be due to, e.g., lung disease; mild hypoxia causes increased cerebral blood flow that is partly compensatory

Ischaemic hypoxia - follows reduced cardiac output, cerebrovascular accident (CVA), and cerebral vasospasm due, e.g., subarachnoid haemorrhage or migraine

The term *delayed post-anoxic encephalopathy* refers to those few cases that 'recover' from a comatose state secondary to hypoxia or ischaemia, enjoy lucidity for days to weeks, and present with delirium and a movement disorder. There is severe demyelination. The basal ganglia are involved to a variable extent. A few patients die or are left demented but most cases improve gradually as far as cognition is concerned but the outlook for disorders of movement, such as parkinsonism or spasticity, is less good.

Cerebral malaria²⁶¹⁴ is present when asexual parasites are found in blood film and patient has impaired consciousness and the cause is not another encephalopathy (e.g. bacterial meningitis or viral encephalopathy). The antimalarial drug mefloquinie (Lariam: half-life 14 days) can cause neuropsychiatric disorders persisting for several days.

Contraindications for mefloquinie therapy

Psychiatric disorder

Epilepsy

Cardiac conduction disorders

Renal/hepatic impairment

First trimester of pregnancy

Lactation

Coma

There are six coma stages: alert, drowsy (responds to verbal commands), unconscious and withdraws from pain, unconscious and decorticate (flexes limbs to pain), unconscious and decerebrate (hyperextension of limbs to pain), and unconscious with zero response.

²⁶¹⁴ **Cerebral malaria:** especially with malignant tertian (*falciparum*) – pyrexia (rarely fever is absent), delirium, severe headache, disturbed behaviour, coma, seizures, retinal haemorrhages, papilloedema, cerebellar ataxia, dysphasia, hemiplegia, and hemianopia may occur.

The *Glasgow Coma Scale* (Jennett & Bond, 1975: see box) is the accepted standard for assessing coma. The score can be given as a single figure (e.g. GCS = 15) or as the response in each of its 3 sections (e.g. GCS = 465).

Glasgow Coma Scale (see text for scoring)	
<i>Item</i>	<i>Score</i>
Eyes open:	
Spontaneously	4
To speech	3
To pain	2
Never	1
<i>Best motor response:</i>	
Obeys commands	6
Localises pain	5
Flexion withdrawal	4
Decerebrate flexion	3
Decerebrate extension	2
No response	1
Best verbal response:	
Orientated	5
Confused	4
Inappropriate words	3
Incomprehensible words	2
Silent	1

Brain death

This may be defined as the irreversible loss of two brainstem functions: the possibility of future consciousness and spontaneous breathing. (Wijdicks, 2001) Such a definition became necessary with the advent of mechanical ventilation and the use of human tissue and organs for transplantation. One must be aware that coma/apnoea due to hypothermia, metabolic or endocrine conditions, electrolyte/acid-base balance/glycaemic problems, sedative drugs, and neuromuscular-blocking agents or other poisons may be associated with recovery after prolonged time periods. Tests used include cranial nerve motor responses to pain, lack of spontaneous breathing despite receiving ventilation with 100% oxygen or 5% CO₂/95% O₂, and corneal/vestibulo-ocular (caloric)/gag or cough/oculo-cephalic (eyes follow head if brainstem intact: doll's eye movements)/pupillary (light) reflexes. Pupils are fixed and can be of any diameter (usually dilated). The presence of spinal reflexes does not negate a diagnosis of brain death. Whilst an isoelectric (flat) EEG would be expected in someone with brain death the EEG is no longer a prerequisite in the determination of that state.

Under normal circumstances the ascending reticular formation (ARF) helps to maintain a healthy cortex in an active mode. Minimally conscious patients show some, rather vague, response to noxious stimuli. Persistent vegetative states follow cerebral cortical damage (e.g. severe trauma) in the presence of a normal ARF/brainstem; the patient appears to be awake but has little or no perception. In the locked-in syndrome the cerebral cortex and ARF are intact but the ventral pons is damaged caudal to the oculomotor nerve nuclei (see box). Irremediable brainstem damage is the equivalent of brain death, i.e. the patient is dead.

Locked-in syndrome (Nordgren et al, 1971)

May follow lesions such as high brainstem infarction or central myelinolysis

Can also follow traumatic brain injury or drug overdose

Normal consciousness (fully aware), tetraplegia, bilateral facial palsy, and paralysis of lateral gaze

Cannot speak or move

Can think and reason

Since vertical gaze is intact, patients may try to communicate with eyes (and eyelids) in a form of Morse

Some general medical disorders²⁶¹⁵

Acute intermittent porphyria (AIP)

AIP²⁶¹⁶ is inherited as an autosomal dominant trait with incomplete penetrance²⁶¹⁷. There is a deficiency of the enzyme porphobilinogen deaminase²⁶¹⁸. In 90% of cases the disease is latent. If enzyme inducers are taken enzymes proximal to the deficient enzyme increase in activity and the concentrations of delta-aminolaevulinic acid and porphobilinogen increase, causing neuronal damage with subsequent myelinolysis.

Precipitants of attacks (O'Shea, 2000; Kauppinen, 2005; Smoller ea, 2008, p. 872; Harrison & Kopelman, 2009, p. 671)

Barbiturates
Luteal phase of menstrual cycle
Oestrogens and progesterone (incl. contraceptive pill and hormone replacement therapy)
Tamoxifen
Anabolic steroids
Dichloralphenazone
Phenylbutazone
Glutethimide
Anaesthetics
Alcohol
Methyldopa
Diclofenac
L-DOPA
Sulphonamides
Erythromycin
Phenytoin
Valproic acid
Carbamazepine
Benzodiazepines
Tricyclic antidepressants
Sulpiride
Fasting
Acute infection
Cocaine
Amphetamines
Smoking²⁶¹⁹

In the absence of a precipitant, the diminished enzymatic activity is usually insufficient to cause a build up of precursors. Relatively safe drugs include aspirin, narcotic analgesics, penicillin, tetracycline, streptomycin, paraldehyde, propranolol, and chlorpromazine and probably clozapine, olanzapine, fluoxetine, paroxetine, and clomethiazole. It is essential to check with manufacturers' prescribing information before giving medicine to patients with porphyria.

Clinical features

²⁶¹⁵ See also Moore.(2001)

²⁶¹⁶ The **porphyrias** are a group of seven rare inherited metabolic disorders, each due to a partial deficiency of a particular enzyme in the haem biosynthesis pathway. The porphyrias include cutanea tarda (most common type worldwide: develops after fourth decade with cutaneous symptoms and chronic liver disease), acute intermittent, aminolaevulinic acid dehydratase deficiency, erythropoietic protoporphyria, congenital erythropoietic, hereditary coproporphyria, and variegate porphyrias. Attacks of acute porphyria may be due to acute intermittent, hereditary coproporphyria, or variegate forms of the disease and these cannot be distinguished clinically.(Kauppinen, 2005) The notion that George III of England (1738-1820) suffered from porphyria is still debated.(O'Shea, 2000) An alternative explanation is arsenic poisoning from medications prescribed by physicians.(Cox ea, 2005)

²⁶¹⁷ Many mutations in PBGD gene in chromosome 11q23.3.

²⁶¹⁸ Uroporphyrinogen-1-synthetase.

²⁶¹⁹ Smoking may be a potential precipitant of porphyric attacks, possibly by altering oestrogen metabolism and induction of hepatic mono-oxygenases.

Acute abdominal pain
 Pains in limbs and back
 Headaches
 Tachycardia
 Nausea, vomiting
 Severe constipation
 Peripheral neuropathy
 Seizures in 20%
 Negative laparotomies
 During attacks: depression, restlessness, abnormal behaviour, organic brain syndromes and psychoses

The diagnosis is made by analysis of the urine (stored in dark and sent rapidly to the laboratory) for porphobilinogen and delta-aminolaevulinic acid. False positive results may occur with phenothiazines, plumbism, and fever. Avoidance of precipitants is essential. Improved carbohydrate intake reverses attacks caused by excessive fasting.

Causes of urine discolouration after it is left standing for some time include porphyria, alkaptonuria, and L-DOPA.

Adrenocortical leucodystrophy

This X-linked disorder presents in adults with adrenal insufficiency, personality change, long tract signs, and dementia.

Alien hand syndrome/sign

Described 1908 by the German Kurt Goldstein

Damage to the corpus callosum and frontal lobes (supplementary motor area)

One of the weirdest experiences in medicine: a hand acts as if it had a mind of its own

Patient says that one hand, nearly always the left, is out of control and behaving independently, sometimes leading to self-harm!

Activities carried out by the hand may be simple or complex

It may reverse movements carried out by the opposite limb, even repeatedly so, e.g. right hand opens a drawer, only for left hand to reverse this manoeuvre

So-called murderous alien hand has been described: as seen in some Hollywood movies, the hand may try to choke its owner or may knock her spectacles off her face!

Interpretations by the patient vary from the neutral ('my hands are in disagreement') to the quasi-delusional ('Martians appear to control my hand').

Some mimics of alien hand:

Asomatagnosia - denial of ownership of a limb

Levitation - simple rising of a limb in parietal damage or progressive supranuclear palsy

Mirror movements - other limb imitates the primary movements of the opposite limb – may be normal or may occur, e.g. in hemiplegics

Grasp reflex

A fuller discussion is provided by Moore.(2001) MacGowan ea (1997) described cases of CJD presenting with alien hand sign.

Alien limb phenomenon

Person complains that he has no control over the movements of the limb

An advanced form of asymmetric limb apraxia: subject knows what needs to be done but cannot perform a simple task such as holding a pen

Ipsilateral rigidity and bradykinesia

Described in cases of corticobasal degeneration, a cause of gradually progressive asymmetric cognitive and motor impairment

Arsenic poisoning

Sources of arsenic: mines, silicon chips, insecticides

Acute cases: GIT symptoms and delirium, perhaps with seizures, and garlic odour from breath; sensory polyneuropathy follows

Chronic cases: dementia, painful polyneuropathy, and cutaneous hyperpigmentation; Mees' lines are transverse white lines in the nails

Insecticides containing high levels of nicotine

Nausea/vomiting/diarrhoea

Tachypnoea

Irritability, headache

Convulsions, coma, death

Asperger's syndrome²⁶²⁰

Clinical features (see Berney, 2004)

'Autism without language disturbance'* (Stone, 1997)

Speech: pedantic, lengthy, stereotyped, aprosodic speech

Impaired non-verbal communication

Peculiar social interaction, socially awkward (gaucheness)

Break the normal rules of social engagement

Talk 'at' rather than 'to' others

May avoid the gaze of others or seem to look through others

Odd or awkward body language

Lack of empathy and sympathy

Resistance to change

Clumsy or stereotyped motor movements

Hypertrophied skills or circumscribed interests²⁶²¹ (e.g. collecting facts and figures of little practical value)

Few friends

*Asperger patients have no delay in general/non-social language development. People with Asperger's syndrome must be distinguished from those with schizoid personality disorder. Teasing may lead to social withdrawal in Asperger cases.

The relationship of Asperger's syndrome to Kanner's syndrome (Q.V.) is controversial²⁶²². (Green ea, 2003, p. 516) Various case reports have suggested different brain changes in Asperger's syndrome, e.g. atrophy of the left temporal lobe or atrophy of central brain areas and cerebellum on the left side. MRI in one study suggested that cerebral grey matter volume is enlarged in autism, with Asperger cases coming between autistic cases and control subjects in this regard. (Lotspeich ea, 2004) This is similar to the MRI findings of Toal ea (2010) who found that frontal and temporal grey matter is increased in autism but not in Asperger cases. McAlonan ea (2009a) found greater white matter volumes (on MRI) around the basal ganglia in high-functioning autism (HFA) than in Asperger's syndrome and these two groups of patients had greater values than were found in controls; HFA children had relatively less frontal and callosal white matter in the

²⁶²⁰ Hans Asperger (1906-1980), an Austrian physician, described this disorder in 1944 under the heading of *Autistischen Psychopathien* or 'autistic psychopathy'. Psychopathy refers here to psychopathology or generic personality disorder.

²⁶²¹ Asperger referred to his patients as 'little professors'.

²⁶²² The Expert Group on Mental Health Policy, (2006, p. 245) among many others, favour placing Asperger's syndrome within the autistic spectrum.

left hemisphere, the same applying to Asperger's syndrome but this time in the right hemisphere. Other MRI work suggests that children with Asperger's or autism interpret faces as if they were non-face objects. Increased prefrontal N-acetylaspartate on MRS appears to correlate with obsessional behaviour. (Murphy ea, 2002) Reductions in cortical 5-HT_{2A} receptor binding have been reported in adult cases that might underlie abnormal social communication. (Murphy ea, 2006) Oxytocin infusions may reduce negative, repetitive behaviours in autism and Asperger's syndrome. (Hollander ea, 2003) There is a report of the presence of a non-DNA mutation (epigenetic) in the gene coding for the oxytocin receptor in autism. (Gregory ea, 2009)

Fitzgerald and Corvin (2001) discuss the diagnosis of Asperger's syndrome in some detail and Fitzgerald (2004) suggests that a wide variety of famous people had Asperger's syndrome. Green ea (2003, p. 516) state that Asperger's syndrome has 'become very popular as a diagnosis among parents and professions... led to overuse... many children with disrupted peer relationships, such as those with ADHD and even early antisocial personality [being] mistakenly diagnosed'.

A primary focus should be on improving social competence, e.g. direct instruction, role play, modelling, social stories (illustrated stories used to determine what people are doing, feeling, and thinking), practice with peers in real-life situations, and use of constructive feedback. (Toth & King, 2008) Skills may be broken down into manageable sub-skills.

Autosomal dominant cerebellar ataxia (spinocerebellar ataxia)

A wide number of mutations involving different genes on different chromosomes have been described, and there are genetic tests for this disorder. Onset is usually in young or middle aged adults, although it can start in children or the elderly. There is atrophy of cerebellum, pons, and inferior olives (MRI should be used). The main features are progressive cerebellar ataxia, dysarthria, and nystagmus. Dementia and psychosis (Rottnek ea, 2008) have been reported. It is different from Friedrich's ataxia, which has a recessive mode of inheritance.

Benign essential tremor²⁶²³

Onset at any age; the most common tremor disorder (chiefly affects the hands); often get a positive family history

Possibly inherited as dominant trait with variable penetrance²⁶²⁴

Often misdiagnosed as Parkinson's disease (Benito-León & Louis, 2007)

Titubation occurs more often than in Parkinson's disease and there is no rigidity or bradykinesia

Usually static or extremely slowly progressive

Predictors of progression include asymmetrical tremor and initially unilateral tremor

May respond to beta-blockers (atenolol, propranolol, nadolol, sotalol), topiramate, primidone, gabapentin, a small amount of alcohol (the patient may become dependent), or benzodiazepines (BZDs)

Botulinum A toxin has been used for hand tremor

Medication-induced postural tremor

A fine postural action tremor may be associated with many drugs, e.g. lithium (increased lithium levels lead to coarsening of tremor, twitches/fasciculation), beta-agonists, dopaminergic drugs, stimulants, caffeine, antipsychotics, antidepressants, and anticonvulsants. Essential tremor, also postural, resembles drug-induced postural tremor. The tremor of drug-induced Parkinsonism is of a lower frequency, is exacerbated by rest, and there will be other features of Parkinsonism. Physiological tremor (low amplitude, due to muscle fibre recruitment during contraction) becomes enhanced (increased amplitude) when muscle contraction is maintained. Such enhanced tremors respond to beta-blockers.

²⁶²³ This is also called essential/familial/senile/juvenile tremor or Minor's syndrome.

²⁶²⁴ Usually the tremor disappears when the limbs are still and in some families tremor is more obvious when performing certain actions, e.g. writing.

Bismuth poisoning

Used for diarrhoea and H pylori infection

Depressed, irritable, or euphoric

Insomnia

Delusions or visual hallucinations (rare)

There may be delirium, tremor, myoclonus, ataxia, or seizures

Carbon disulphide poisoning

Used as a solvent (rubber and viscose rayon industries) and in various insecticides

Can cause mixed polyneuropathy, Parkinsonism, CVA, headache, dizziness, diminished libido, anorexia, psychosis, poor attention/memory/vigilance, impaired psychomotor skills, and visuospatial dysfunction

Slowly developing personality change has been reported, e.g. unstable moods, temper attacks, apathy

There may be diffuse leucoencephalopathy

Carbon monoxide poisoning

CO is colourless and odourless

Classically (but uncommonly) the patient is cherry-red, commonly there is cyanosis

Commonly occurs accidentally in environments subject to defective heating or exhaust ventilation; may be taken deliberately by inhaling car exhaust fumes; methylene chloride in paint strippers is converted to CO

Early symptoms are headache, nausea, dizziness, tiredness, malaise, cough, weakness, disorientation,

hyperventilation (a flu-like presentation), followed by psychosis, delirium, seizures and coma

Chronic low-level exposure causes depression and cognitive dysfunction

Acute cases may die or recover fully

About 2% of survivors have chronic sequelae such as Parkinsonism and a Korsakoff-like amnesic state following coma and delirium

Other permanent effects include disorientation, moodiness/irritability/aggressiveness, memory problems, cortical blindness, ataxia, and apraxia

Dysmnestic syndromes usually recover if due to subarachnoid haemorrhage but outlook is less certain if the cause is cerebral hypoxia, e.g. CO

Globus pallidus, hippocampus and cerebral cortex show patchy cell loss

May be confluent areas of demyelination in deep white matter of cerebral hemispheres

Management: remove patient from exposure source; normobaric oxygen (some work suggests that hyperbaric oxygen is better, but this is controversial: see Weaver, 2009); identify and eliminate source

Charles Bonnet syndrome

This is an uncommon disorder²⁶²⁵ due to ongoing neural activity in the visual system (that is lacking stimulation from the sense organ). Classically there are dynamic, colourful, mute and pleasurable visual hallucinations with full insight into their hallucinatory origin. Consciousness is clear. It is associated with eye (macular degeneration, glaucoma, cataract – but vision can be normal) rather than cerebral disease.

Activity has been recorded in the ventral extrastriate cortex during visual hallucinations in such cases, and the content of hallucinations (e.g. colour) activated the appropriate cortical area.(Blakemore, 2002)

Management is that of the eye disease, explanation, reassurance that the patient is not mentally ill, increased domestic lighting, reducing social isolation, and, much less certainly, atypical antipsychotics and anticonvulsants. Some cases get relief when complete blindness is reached.(Jacob ea, 2004)

Auditory variant of Charles Bonnet syndrome

Persistent auditory hallucination (often musical – choirs, show bands, choirs, etc), with preserved insight, in the absence of cognitive decline. Management is as for the visual variety.

²⁶²⁵ The syndrome was described in 1760 by the Swiss philosopher Charles Bonnet (1720-90) who observed it in his grandfather.

Choking

Choking as a problem in psychiatric patients was recorded during the nineteenth century, (Warner, 2004) well before the advent of modern psychotropic drugs. 218 Irish psychiatric inpatients died suddenly or unexpectedly during 1983-92, 22 (10%) from asphyxia: 14 choked²⁶²⁶ and 8 aspirated. (Corcoran & Walsh, 2003) The Heimlich manoeuvre was difficult to use in obese cases. The authors suggest checking for (and investigating) dysphagia, supervision at meal times, review of anticholinergic (impaired gag reflex) and neuroleptic drugs, staff education²⁶²⁷, and consideration of feeding by gastrostomy for patients with cognitive impairment and recurring choking episodes.

An Australian study (Ruschena *et al.*, 2003) found that risk of choking is increased in schizophrenia and organic psychiatric illness. The risk was increased if the patient was treated with thioridazine or lithium. Tardive dyskinesia (TD) may be a factor in choking, as may possibly be schizophrenia itself because of impaired swallowing. (Goff & Shader, 2003, p. 579; Warner, 2004) Eating habits, such as eating too fast, may be a factor in choking. Because choking deaths are rare, determining magnitude of any risk found is problematic.

Chorea²⁶²⁸

Non-repetitive, jerky, semi-purposeful, face and trunk movements usually caused by lesion in caudate nucleus. Causes include genetic (e.g. Huntington's disease), infective (encephalitis, Sydenham's chorea), drugs (L-DOPA, phenothiazines – also a cure!), metabolic (pregnancy, anovulants, hyperthyroidism, hypoparathyroidism), and vascular (SLE, polycythaemia). Treatment includes dopamine (DA) receptor antagonists (neuroleptics), DA depletion (tetraabenazine, reserpine), and GABA enhancement (sodium valproate).

Morgan syndrome

Potentially fatal, fibrillary chorea of probable autoimmune causation
Can occur as a paraneoplastic condition
Characterised by involuntary activity of muscle fibre, excessive sweating, and insomnia

Chorea gravidarum

Chorea may be induced by pregnancy or by the contraceptive pill
May have been a childhood history of Sydenham's chorea

Benign familial chorea (hereditary chorea without dementia)

Rare autosomal dominant disorder with no intellectual decline
Usually starts in childhood – usually does not progress further in adulthood, but can do so
Head, face and upper limbs chiefly affected
Must be differentiated from Huntington's disease

Cleft lip and palate

Numerous potential factors of psychiatrist interest may influence the development of these anomalies although the weight of evidence is not strong for some: maternal smoking (alcohol less consistently) during pregnancy, folate and zinc deficiency, anticonvulsants (especially benzodiazepines, phenobarbital, and phenytoin), corticosteroids, first trimester viral infection, and numerous genetic syndromes. (Mossey *et al.*, 2009)

Compulsive water drinking

²⁶²⁶ Average age 51 years, which is younger than fatal choking cases in the general population; 12 were in hospital for > 5 years; main ICD-9 diagnoses: 4 organic psychoses (2 had frontal lobe atrophy at autopsy), 3 intellectually disabled, 6 schizophrenic, and 1 bipolar affective disorder.

²⁶²⁷ Long-handled forceps, mechanical suction, cricothyrotomy needles, and Mendlesohn manoeuvre.

²⁶²⁸ Gk, *choreia*, dancing: as in choreography.

Trainees in psychiatry who spent time in older psychiatric institutions saw chronic schizophrenic patients with their heads under the taps drinking large quantities of water. This led to haemodilution and hyponatraemia. Why institutionalised patients, with a wide variety of diagnoses, should drink excess water is poorly understood. It may partly be iatrogenic (xerostomia secondary to drugs) or a result of their psychopathology ('psychogenic [primary] polydipsia') or boredom. Psychogenesis is far from proved. Some patients will drink bath water or urine if they cannot get anything else. Many drugs may contribute, e.g. nicotine, thiazide diuretics, carbamazepine, chlorpropamide, tolbutamide, clofibrate, cyclophosphamide, and vincristine. Delusions may underlie some cases. Supervision, monitoring of weight, occupation, social activities, and attention to medication if possible should help. Initially, water restriction is essential. It should not be confused with nephrogenic diabetes insipidus (*giving ADHD for compulsive water drinking may exacerbate water overload and cause hyponatraemia*). Increasing the dose of neuroleptic may actually reduce water consumption. (Crammer, 1991) There is some early evidence that clozapine may reduce water consumption in psychiatric patients. (see Goff & Shader, 2003, p. 576)

A normal adult can excrete 15 litres of water daily, but retention of water occurs if intake exceeds this rate. Water retention may be due to the syndrome of inappropriate secretion of antidiuretic hormone. (Q.V.)

Effects of water intoxication (WI): hyponatraemia, and encephalopathy (restlessness, confusion, lethargy, nausea, diarrhoea, vomiting, muscle twitching, ataxia, convulsions, stupor, coma, and even death)
Complications of WI: recurrences of same, bowel and bladder dilatation, hydronephrosis, renal failure, malnutrition, projectile vomiting, cardiac failure, dementia, hernias, incontinence, and spinal fractures due to loss of calcium

Hyponatraemia from water intoxication may be missed unless blood is drawn in the afternoon. In established water intoxication all fluid intake should be stopped and urinary excretion should be awaited. Over enthusiastic correction of hyponatraemia may be a cause of pontine demyelination.

Diabetes insipidus (DI, 'watery sieve'²⁶²⁹)

ADHD (vasopressin) normally binds to the V2 receptors in renal collecting tubules. This action stimulates adenylate cyclase with the eventual insertion of aquaporin water channels. More water is reabsorbed and urine is concentrated. Polyuria leads to polydipsia in DI. In central DI²⁶³⁰ there is not enough ADHD coming from the neurohypophysis whereas in nephrogenic DI ADHD action on the kidneys does not lead to the expected response²⁶³¹. DI should not be confused with diabetes mellitus, psychogenic polydipsia, renal disease, and excess water intake due to phenothiazines. The primary problem in DI is water loss whereas that in psychogenic polydipsia is excess water intake. Nocturia is much more common in DI than in psychogenic polydipsia.

Compulsive utilisation (utilisation behaviour)

In compulsive utilisation, a frontal lobe disorder, the patient will employ anything to hand even whilst knowing that they should not do so. Lhermitte (1983) gave the example of the patient who put on three pairs of spectacles at the one time simply because they were available! Joseph (1996) illustrates compulsive utilisation by the example of a patient who has a hammer and nail placed in front of him and is told not to use them: he never the less hammers in the nail. A patient might see a hypodermic syringe and inject the examining physician! (Baddeley, 2008) A more mundane example would be a person inappropriately drinking someone else's tea.

Differential diagnosis

Alien hand

Mitgehen - patient moves in the direction of even slight pressure despite being told to resist

²⁶²⁹ As distinct from diabetes mellitus or 'sweet sieve'.

²⁶³⁰ The aetiology of central DI includes head injury, surgery, tumours of hypothalamus, TB, sarcoidosis, familial, and idiopathic.

²⁶³¹ The aetiology of nephrogenic DI includes lithium, excess calcium, longterm excess water intake, hypokalaemia, and genetic.

Forced grasping/groping - frontal lobe damage causes person to grope/grasp object seen/felt
Paradoxical intention - psychological ploy e.g. telling a couple to keep fighting in order to stop them arguing

Corticobasal ganglionic degeneration (CBD)

A mostly sporadic condition lasting 4-10 years before death, CBD starts as an asymmetric cortical atrophy in the parietal and posterior frontal lobes and spreads from there. There are neuronal loss and astrocytosis, with abnormal filaments in ballooned cells. This progressive, incurable condition starts in the seventh decade with asymmetric rigid akinetic Parkinsonism of an upper limb (dystonia may mask this presentation in some cases) that is refractory to levodopa. It presents with difficulty carrying out some movement functions. At least half of cases eventually become demented. Yoclonus, postural instability, and alien hand sign may occur. Tau²⁶³² protein (64 and 68 kDa) accumulates in a number of cerebral areas. In some families there are reports of mutation of the tau gene.

Dentatorubropallidolusian atrophy

This is inherited as an autosomal dominant trait with an expanded trinucleotide (CAG) repeat at 12p12-13²⁶³³. Like Huntington's disease, dentatorubropallidolusian atrophy is a polyglutamine disorder. There is neuronal loss and gliosis, especially in dentate and red nuclei, globus pallidus, 'corpus Luysii' (i.e. subthalamic nucleus), and other areas. It may commence in childhood or adulthood. The commonest presentation in adults includes ataxia, chorea, and dementia. Children often have dementia and myoclonus. It is a progressive disorder.

Domoic acid poisoning (Cendes ea, 1995)

Very rare sequel to ingesting mussels
 Domoic acid is excitotoxic
 Can cause atrophy of hippocampi and complex partial seizures

Disintegrative disorder (disintegrative psychosis of childhood, Heller's syndrome)

This condition was described by the Austrian educator Theodore Heller in 1908 as *dementia infantilis*. A previously normal child, more commonly a boy, undergoes massive regression between 2-10 years of age. There is severe acquired autism (early normal development distinguishes it from Kanner's syndrome), (usually) loss of cognitive skills, and no evidence of brain degeneration or schizophrenia. Epilepsy may complicate the picture. Rapin (1997) and Green ea (2003, p. 515) include it in the autistic spectrum. The disorder is 60 times rarer than Kanner's syndrome, the prevalence being about 22/million.(Hussain, 2007) Despite claims in the early literature, an association of childhood disintegrative disorder with specific underlying medical/neurological diatheses has not been upheld.

Dystonias

There are various dystonic syndromes. (Drug-induced dystonias are not discussed here.) They are caused by abnormal brain function, usually in the basal ganglia. It has been suggested that dystonia is due to release of premotor cortex from thalamic control. They used to be considered 'psychogenic' in origin. There are sustained muscular contractions affecting almost any part of the body, frequently causing twisting or repetitive movements or abnormal postures.

Different syndromes are frequently named according to site affected, e.g. blepharospasm, writers cramp, and spasmodic torticollis

Usually starts in one part of body as focal dystonia
 All dystonic movements and postures are exacerbated by attempts to move
 May be progressive, especially when starting in a young person

²⁶³² Tau gene is on chromosome 17.

²⁶³³ The gene is called atrophin. Surviving nerve cells contain intranuclear inclusions consisting of abnormal atrophin-1.

Progression is to segmental or multifocal dystonia, or even generalised dystonia
 Hemidystonia is due to structural cause in > 80% of cases, e.g. stroke, head injury, or brain tumour
 Wide range of disorders can cause secondary dystonia, e.g. Huntington's disease, Wilson's disease²⁶³⁴,
 Parkinson's disease, Lesch-Nyhan syndrome, head trauma, homocystinuria, kernicterus, viral encephalitis,
 arteriovenous malformations, ataxia telangiectasia, neuroleptics and wasp stings
 Drugs causing acute dystonia include neuroleptics (including atypical antipsychotics), SSRIs,
 metoclopramide (antiemetic substituted benzamide), and certain antihistamines (e.g. used to combat
 seasickness)
 Buspirone can lead to persistent dystonia (LeWitt ea, 1993)
 Clozapine can reduce drug-induced dystonia, it can trigger dystonia (responds to anticholinergics or BZDs),
 and dystonia can occur during clozapine withdrawal (Lauterbach, 2000)

Success has been achieved in spasmodic torticollis (wryneck) by injecting botulinum toxin (binds permanently to nerve endplates, blocking Ach (acetylcholine) release – recovery over 8-12 weeks as new endplates grow – may need repeat injections up to 6 times per year) into the contralateral sternocleidomastoid and the ipsilateral splenius muscles.

Blepharospasm

Involuntary closure of eyelids
 Was often mistakenly seen as a form of conversion hysteria
 Primary cases occur alone (essential blepharospasm) or involve other parts of the face or body as well (Meige syndrome²⁶³⁵)
 May be secondary to eye disorders (e.g. conjunctivitis or disease of the cornea) or neurological disease, especially disorders of the brainstem and the basal ganglia (e.g. encephalitis lethargica, focal lesions, Parkinson's or Huntington's diseases)
 Neuroleptics may cause it
 Depression found in up to 30% of cases
 There is sometimes a family history of blepharospasm

Dopaminergic activity is important in regulation of blinking, and spontaneous blink rates are affected by several disorders, e.g. they are reduced in Parkinson's disease and increased in schizophrenia. Owens (1990) suggested that the Pisa syndrome is simply a form of tardive dystonia. Owens (2000) is a useful source of up to date information.

Bilateral stimulation of the internal globus pallidus improves primary generalised dystonia. (Vidailhet ea, 2005) Much more needs to be learned about this treatment ('deep-brain stimulation') before it can be recommended for other than refractory, severe cases. (Greene, 2005)

Dystonia Ireland²⁶³⁶ lists identified inherited dystonias as early-onset generalised dystonia (generalised/idiopathic torsion dystonia: most cases relate to DYT1 gene; twisting of distal limbs), dopa-responsive dystonia (Q.V.), paroxysmal dystonia (attacks of 'kinesigenic' dystonia that are brief and precipitated by sudden movements, or frequent and prolonged paroxysms of dystonic choreoathetosis), X-linked dystonia-Parkinsonism (on Philippine island of Panay; Xq13; focal then tonic dystonia progressing to Parkinsonism), myoclonic dystonia (jerks +/- more sustained contractions/postures), and rapid onset dystonia-Parkinsonism (abrupt onset). The focal dystonias are listed as blepharospasm, cervical dystonia (spasmodic torticollis), embouchure dystonia (affects brass and woodwind players), oro-mandibular dystonia, spasmodic dystonia (affects vocal cords), writer's cramp, and hemifacial spasm (not a true dystonia: irritation of VII nerve causes irregular unilateral facial muscle contraction). As well as these there are the secondary dystonias (*vide supra*). Significant advances have been made in the genetics of dystonia,

²⁶³⁴ Any young patient with hepatic dysfunction, movement disorder, and psychiatric symptoms (or any 2 of these) should be tested for Wilson's disease. Bizarre dystonic posturing may be dismissed as 'psychiatric'.

²⁶³⁵ Described in 1910 as *spasme faciale mediane*.

²⁶³⁶ Tel: 00-353-01-4922514. Fax: 00-353-01-4922565. E-mail: info@dystonia.ie. Web Page: www.dystonia.ie.

e.g. the DYT1 gene and Torsin-A protein (due to a GAG deletion) responsible for early-onset childhood dystonia.

Behavioural approaches such as EMG biofeedback may help. Drugs may be tried, e.g. clonazepam, baclofen, anticholinergic agents, and pimozide. Reducing or stopping neuroleptics, where possible, may help. Reserpine and tetrabenazine, DA depleting agents, have been used but are associated with depression and Parkinsonism. Myectomy and other surgical techniques have been employed. However, no drug is universally affective. Botulinum toxin injected around the eye may give relief for a few weeks but may cause a transient ptosis.

Influenza encephalitis

Usually lasts for days only

May be more common in children

EEG usually shows diffuse abnormality

Headache, vomiting, confusion, coma

Transient limb weakness/reflex changes

Post-viral depression

Less common: hallucinations, transverse myelitis and other spinal/nerve root problems, Guillain-Barré-like syndrome

Encephalitis lethargica (European sleeping sickness, Von Economo's disease²⁶³⁷, EL)

Delirium is followed by drowsiness²⁶³⁸. There may be personality change, obsessional states, oculogyric crises and Parkinsonism. It is due to damage to the substantia nigra, probably caused by influenza A virus. Lymphocytes infiltrate the brain. There is perivascular cuffing and gliosis. Any age group may be affected. Muscles are rigid, tremor is less than in Parkinson's disease, the skin is oily, sialorrhoea occurs, convergence problems are common, and many of the psychiatric problems are transient. EL has become very rare since the epidemic following the 1914-18 war. The Parkinsonian syndrome tends to remain static over time.

Friedreich's ataxia

9q13; expanded triplet repeat (GAA); Frataxin-intronic gene; recessive inheritance

Occasionally accompanied or preceded by schizophrenia-like psychosis with or without violent behaviour

Adult Gaucher's disease

Glucocerebrosidase deficiency (chromosome 1q21-22) and glucocerebroside accumulation in CNS and reticuloendothelial cells

May present with ataxia, behaviour problems, dementia and psychosis

Pantothenate kinase-associated neurodegeneration²⁶³⁹

Autosomal recessive

2 variants: type 1 (mutation of PANK2 gene), type 2 (PLA2C6 gene)

Atrophic, rusty brown (due to iron accumulation) globus pallidus

'Eye of the tiger' sign - decreased and increased signal intensity in the external and internal segments of the globus pallidus respectively on T2-weighted MRI scans

Wide range of age of onset, most often in children and adolescents

Extrapyramidal syndromes

Dementia supervenes

Death in 10-15 years

²⁶³⁷ Described in 1917 by Baron Constantin Von Economo (1876-1931): born in Trieste, studied and worked in Vienna; student of Wagner-Jauregg; did research on mechanism of swallowing.

²⁶³⁸ Von Economo described (a) a brief prodrome of fever and sore throat followed by (b) one of a number of acute presentations (somnolent-ophthalmoplegic, hyperkinetic, Parkinsonian, or any combination of these occurring in any order); all these were accompanied by various neurological disturbances (trismus, seizures, cerebellar signs, aphasia, neuralgia, ptosis, etc); acute cases could be associated with delirium, hypomania, oneroid states, and apathetic depression; and (c) chronic cases were associated with Parkinsonism (often with catatonic phenomena), oculogyric crises, and psychiatric (depression, mania, schizophrenia-like) problems. (McKenna, 2007, pp. 390-395)

²⁶³⁹ This was called *Hallervorden-Spatz disease* but Julius Hallervorden (1882-1965) and Hugo Spatz (1888-1969) received brains from the Nazi euthanasia programme and they have become written out of history!

Schilder's disease (diffuse cerebral sclerosis)

Rare demyelinating condition, sporadic and familial, rapidly fatal, may represent severe early-onset MS

Mostly occurs in children but may affect adults

Schizophrenia-like psychosis, paralysis, blindness, deafness, apathy, dementia, stupor, papilloedema

Greyish or brownish softening of white matter, especially occipital

MS-like CSF findings and smaller CNS lesions are same as in MS

Hashimoto's disease

High titres of anti-thyroid antibodies

Can affect either thyroid (thyroiditis with transient hyperthyroidism) or brain

Cerebral Hashimoto's disease (Hashimoto's encephalopathy²⁶⁴⁰) can cause delirium, myoclonus, and various seizure types or dementia (often with psychotic features) – there are high serum antithyroid antibody levels and it responds to corticosteroids (Chong ea, 2003)

Hereditary mental depression and Parkinsonism (Perry syndrome: Perry ea, 1975)

Rare, rapidly progressive, familial condition (autosomal dominant) with taurine deficiency

Severe neuronal loss in substantia nigra, without alpha-synuclein or tau pathology

Loss of NK-1R and TH immunoreactive neurones in ventrolateral medulla and 5-HT neurone loss in medullary raphe and ventrolateral medulla

Dyneclin (DCTN1) mutations (Farrer ea, 2008) causing diminished microtubule binding and introcytoplasmic inclusions

Midlife depression eventually complicated by progressive Parkinsonism

Weight loss

Respiratory failure (central hypoventilation) ensues; death in 2-10 years

Hereditary progressive (DOPA-responsive) dystonia

Rare, dominant (chromosome 14q) disorder

Worsens as the day wears on

Reduced level of tetrahydrobiopterin (co-factor for tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis)

Herpes simplex encephalitis²⁶⁴¹

The virus (HSV-1)²⁶⁴² affects the cortex of the medial temporal lobes and the orbitofrontal cortex. There is widespread cellular destruction and Cowdry type A inclusion bodies may be found in affected nerve cells. The patient quickly becomes very unwell. Classical symptoms include pyrexia, confusion, changes in behaviour, somnolence, amnesia, and partial complex seizures. There may be sensory problems, visual field defects, aphasia, and cranial nerve dysfunction. Delirium, often resembling DTs, proceeds to coma. Restless overactivity may follow recovery from coma. Mortality rates fell from 7 to 2 out of ten cases with the advent of antiviral drugs. If the patient survives there may be dementia (intellectual disability in children) with dysphasia, personality change, a Klüver-Bucy syndrome or a Korsakoff-like syndrome. Less common are emotional lability and schizophrenia-like psychosis. Following a non-specific phase, the EEG demonstrated *episodic* epileptiform temporal lobe activity. MRI shows high signal in the temporal lobes on T₂-weighted scans. The CSF has raised white cell numbers. PCR of CSF for herpes simplex DNA is positive in most (95%) cases, brain biopsy only being needed if CSF cannot be obtained. IV acyclovir should be used early. Valacyclovir is an alternative drug. Foscarnet may be needed in the immunocompromised since such patients may be resistant to acyclovir. Dexamethasone and mannitol are useful for cerebral oedema, but cerebral decompression may be required. Anticonvulsants are used for seizures. There were some early scares that fluoxetine might reactivate herpes infection. (Reed & Glick, 1991)

²⁶⁴⁰ First reported by Brain ea. (1966)

²⁶⁴¹ In general, some cases of viral encephalitis, of which HSV-1 is an example, can have a psychopathological rather than a neurological presentation, e.g. psychotic depression, mania, other psychosis or catatonia. There may be a mistaken psychiatric referral. In such cases there is an increased risk of extrapyramidal side effects (EPS), catatonia, or neuroleptic malignant syndrome (NMS) from use of antipsychotic drugs.

²⁶⁴² HSV-1 and HSV-2 are associated with labial (cold sore) and genital herpes respectively.

AIDS patients may be severely affected with severe haemorrhagic encephalitis and even an ascending myelitis. Other causes of encephalitis need to be considered, e.g. mumps and arbovirus. Type B HSV virus²⁶⁴³ is transmitted by the bite or scratch of a monkey (or even a splash in the eye) and is fatal in about 80% of cases.

Herpes zoster virus

This may invade the central or peripheral nervous system in AIDS patient and cause diffuse encephalitis. Neuronal and glial eosinophilic inclusion bodies indicate the presence of the virus.

Brain abscess

This may be disarmingly silent although the great majority of cases will have a source of infection that varies from middle ear infection to bronchiectasis²⁶⁴⁴. The patient may feel unwell, with some change in personality or minimal confusion. Headache, when present, may be unremarkable. Fever may not occur in longstanding cases. Because of the gradual nature of abscess expansion, intracranial pressure may be little affected and papilloedema may be a late finding. At a later stage the abscess may simulate a neoplasm with worsening headache, seizures (epilepsy in one-third of cases), personality change, and focal signs (depending on location, e.g. anosmia if the frontal lobe is involved). Meningism may be manifest. Rupture may be fatal. Lumbar puncture is unlikely to add much and carries a risk of coning. CT is usually adequate to make the diagnosis (ring-shaped hyperdense area with surrounding oedema). Treatment involves aspiration, excision, and antibiotics. Outcome is variable and epilepsy is a common sequel.

Hydrocephalus

This can be of one of three types: non-obstructive, communicating (secondary to brain atrophy), obstructive and non-communicating (secondary to blocked CSF flow within the ventricles), and obstructive and communicating (normal pressure hydrocephalus - secondary to a block of CSF flow in the subarachnoid space or failure of normal absorption).

Hydrogen sulphide (sewer gas) poisoning

Gas smelling of rotten eggs

Exposure in leather tanning, oil refining, and sourgas field work (natural gas production)

Interferes with cellular respiration, causing hypoxia

Exposed person can lose consciousness ('knockdown') and die or be left with permanent neurological sequelae

Motor signs include ataxia and tremor

Neurological symptoms may appear after apparent recovery

Less severe exposure can cause mucous membrane irritation, headache, nausea, confusion, dizziness, dyspnoea, chest pain, and bradycardia

Hyperekplexia (familial startle disease, Kok disease)

Rare hereditary disease that may be associated with mutation in glycine receptors

Excessive startle to unexpected noise, movement, or touch

Hypertonia, falling stiffly like a log, hyperreflexia, and unsteady gait may occur

Inappropriate antidiuretic hormone secretion (IAHS)

This has been reported in association with a wide variety of drugs, including carbamazepine, dothiepin, lofepramine and fluoxetine. The early symptoms of hyponatraemia (confusion, weakness, etc.) may mimic a psychiatric condition.

²⁶⁴³ Human infection with this neurotropic virus is very rare. Manifestations include a blister at the site of the bite, necrosis in many organs including brain, and, in many cases, ascending paraplegia. Following the death of a doctor in 1932, Albert Sabin (1906-1993) identified an unfilterable agent from autopsy material.

²⁶⁴⁴ The chief pathogens are streptococci, staphylococci, and E coli.

Rett's²⁶⁴⁵ syndrome/disorder

This is almost confined to females, is X-linked with mutation in the MeCP2 gene²⁶⁴⁶ in most classic cases, and has a prevalence of 0.8/10,000 girls. There is initial normal development during first months, then slowing of head growth, stereotypies (wringing/clapping of hands), truncal/limb ataxia, loss of interest in surroundings, severe language problems (expressive and receptive), psychomotor slowing, intellectual retardation.

Austistic disorder (autism, infantile autism)²⁶⁴⁷

The boundaries of this non-mendelian disorder(s) are not clear. Hence terms varying in restrictiveness from 'core autism' via the wider 'autistic spectrum disorders' and 'pervasive developmental disorders'. (Green ea, 2003, p. 503) Rapin (1997) described DSM-IV's pervasive developmental disorder (PDD) as 'the spectrum of autism' and divided it into autistic disorder/classical autism, Asperger's syndrome, pervasive developmental disorder not otherwise specified (perhaps the most common PDD), Rett's disorder and childhood disintegrative disorder (Q.V.). DSM-IV-TR does not allow a separate diagnosis of ADHD in the presence of a pervasive developmental disorder even when the diagnostic criteria for ADHD are present²⁶⁴⁸. Kanner²⁶⁴⁹ described autistic disorder, an idiopathic condition, in 1943. Prevalence among schoolchildren was said to be about 0.02-0.04%. Reported increases to 0.2-0.5% of schoolchildren may be due to more active search for cases and changes in diagnostic criteria, (Rapin, 2002; Green ea, 2003, p. 513; Honda ea, 2005) although a true increase cannot be ruled out. (Lauritsen ea, 2004) The prevalence of childhood autism in the Eastern Health Board area of Ireland²⁶⁵⁰ was estimated by McCarthy ea (1984) to be 4.31/10,000 (0.04%) children. These authors divided the 28 affected children on the multi-axial classification system into 3 groups: classical nuclear autism (50%), autism and profound intellectual disability, and autism and equally significant biological and/or psychosocial factors (21%). It is about 3-4 times more common in boys than in girls and can start any time during the first 24 months of life. Increasing numbers of children being diagnosed with autism in the UK during 1992-2000 may be related to a 20% drop in those diagnosed as having 'behavioural' and 'developmental' disorders matched by a 20% increase in those given the label of 'autism', i.e. a shift in diagnostic habit. (Jick & Kaye, 2003) Recent UK estimates of prevalence among pre-school children were 16/10,000 for core/classic autism and 62/10,000 for pervasive developmental disorders. (Chakrabarti & Fombonne, 2001) Again, such high figures might represent changes in approach to diagnosis rather than any real increase in numbers. Baron-Cohen ea (2009) in the UK estimate that the ratio of known to unknown cases of autism spectrum conditions is about 3 to 2 and, based on a school-based survey, that the spectrum prevalence is 157/10,000.

Numbers diagnosed with autism spectrum disorders over two decades increased by a factor of ten, from one in 4,000 to at least one in 400. (Honda ea, 2005) There is a seven-fold difference between the various US states in diagnosis rates. Bishop ea (2008) suggested that some adults diagnosed in childhood with developmental language disorder would now be diagnosed with autistic disorder.

The child may appear normal prior to its onset²⁶⁵¹. Parents have been reported as being of high intelligence and non-autistic relatives may have an excess of cognitive and speech problems. In reality there is no social class bias. The early notion of emotionally cold parents as a cause of this condition has been jettisoned unceremoniously.

Gardener ea (2008) conducted a meta-analysis and found insufficient evidence to state that any one prenatal factor is causative of autism. However, there was some evidence suggesting an increased risk if the patient was exposed to pregnancy complications. An association between having an older father and increased risk (1.8) for high-functioning autism has been reported from Japan. (Tsuchiya ea, 2008) There is evidence for increased paternal age in the genesis of autism spectrum disorder, whether through fresh mutations or

²⁶⁴⁵ Andreas Rett (1924-1997) a paediatrician in Vienna described this disorder in 1966.

²⁶⁴⁶ Encoding X-linked methyl-CpG-binding protein 2: in Rett's syndrome there is disruption of MeCP2 which is a protein that binds to methylated DNA.

²⁶⁴⁷ Gk. self. Also known as Kanner's syndrome or primary autism or childhood autism or simply 'autism'.

²⁶⁴⁸ This is at odds with the statement in *A Vision for Change* (Expert Group on Mental Health Policy, 2006, p. 245) that 'autism is no longer considered to be primarily a mental disorder'.

²⁶⁴⁹ Leo Kanner (1894-1981), born Austria and worked at Johns Hopkins Hospital, Baltimore. His original sample was subject to referral bias which probably explains why he associated autism with more successful parents!

²⁶⁵⁰ Later, and briefly, the Eastern Regional Health Authority, centred on Dublin.

²⁶⁵¹ However, the infant may show limited eye contact, little smiling or facial responses, and a dislike of being held. Mild variants (here one might include Asperger's syndrome) may not be recognised until just before or after starting school. (Tantum, 1988)

altered genetic imprinting.(Reichenberg ea, 2006) Previous studies, of different methodologies, had suggested a connection between older fathers and risk for autistic-spectrum disorder in offspring, including cases with intellectual disability, although not all studies confirm this association.(Larsson ea, 2005) There is no scientific evidence for a connection between autism or Crohn's disease and the MMR ('triple' or measles, mumps and rubella) vaccine²⁶⁵².(Anonymous, 2002a; Taylor ea, 2002; Chen ea, 2004; Smeeth ea, 2004; Baird ea, 2008; Charatan, 2009²⁶⁵³) There is some evidence for poor hearing, other perceptual difficulties, general cerebral dysfunction, receptive dysphasia, and a genetic element with variable penetrance. There is some preliminary evidence for accelerated head growth in infancy.(Courchesne ea, 2003) Israeli suggestions of a link between in vitro fertilisation (IVF) and autism (see Barron, 2010) are very preliminary and must take into account the relatively greater age of the mothers and higher incidences of prematurity and low birth weight. Autosomal recessive inheritance has been suggested. The pooled frequency of autism in the siblings of autistics is about 2.7%, 50 times that in the general population.(Le Couteur, 1990) It may be neuropathologically heterogeneous²⁶⁵⁴. Identical (MZ) twins concordant for autism and with obvious evidence of perinatal brain damage have been reported. The increased reports of obstetric complications may reflect foetal abnormality rather than aetiology.(Glasson ea, 2004) MZ co-twins are more likely to be concordant for autism as are DZ co-twins, 65% versus 0% respectively.(Pericak-Vance, 2003) Even though autistic people rarely have offspring the condition does not die out, suggesting that autism is only part of the potential phenotype. The genotype may be passed on via those with milder phenotypes (social and communication deficits and stereotyped behaviour has been reported in families where more than one sibling was autistic). Mutations in genes encoding neuroligins²⁶⁵⁵ might be involved in autism.(Chih ea, 2004) Deletions within the neurexin 1 gene on chromosome 2p have been reported in autism and in schizophrenia.(Rujescu ea, 2008) According to Guilmatre ea (2009) weakly to moderately recurrent copy number variations (CNVs), transmitted or occurring *de novo*, might have an aetiological or contributory role in autism, schizophrenia, and intellectual disability. Pinto ea (2010)²⁶⁵⁶ found in autism spectrum disorders a higher global burden of rare (< 1% frequency) CNVs compared to controls, especially for loci previously implicated in ASD and/or intellectual disability; there were a number of *de novo* and inherited events among the CNVs, sometimes in combination in a given family; many novel autism spectrum disorders genes (e.g. SHANK2, SYNGAP1, DLGAP2, and the x-linked DDX53-PTCHD1 locus) were implicated; and there was enrichment of CNVs disrupting functional gene sets involved in cellular proliferation, projection and motility, and GTPase/Ras signalling. Ramoz ea (2004) reported linkage and association between autistic disorder and two SNPs on chromosome 2q.²⁶⁵⁷ This suggests involvement of the aspartate/glutamate carrier. Weiss ea (2008) reported a microdeletion and microduplication on chromosome 16p11.2 that might account for 1% of cases²⁶⁵⁸. A large genome-wide study (Wang ea, 2009) reported an intergenic region between cadherin²⁶⁵⁹ 9 and 10 on chromosome 5p14.1 in autism spectrum disorder patients. About 2 of 3 cases are mentally retarded.²⁶⁶⁰ Affected children may appear superficially normal and perform deceptively well in some areas, such as constructional tasks or music. They may exhibit catastrophic reactions when attempting a task. They appear to inhabit a world of their own. 20%-25% of autistic children will develop seizures by the age of 18 years, usually starting in adolescence (especially likely if there is severe intellectual disability).

²⁶⁵² This hasn't stopped litigants being recompensed in the US.(Offit, 2008)

²⁶⁵³ US Court of Federal Claims rejected a connection with autism in 2009. Andrew Wakefield, the UK gastroenterologist who started the MMR controversy, was struck off by the GMC in 2010.(Kmietowicz, 2010)

²⁶⁵⁴ E.g. **Timothy syndrome** is an excessively rare autosomal dominant disorder with syndactyly, long QT, cardiac arrhythmias and malformations, and, in half of cases, facial dysmorphism. Autism or autistic spectrum disorder may be found. The average age at death is 2.5 years. Mutations occur in the CACNA1C gene on chromosome 12p.13.3.

²⁶⁵⁵ A synaptogenic substance involved in pre- and post-synaptic differentiation.

²⁶⁵⁶ The research group included TCD involvement, e.g. Michael Gill.

²⁶⁵⁷ These findings are not universal.(Rabionet ea, 2006)

²⁶⁵⁸ 16p contains an excess of 'recent' duplications from the evolutionary standpoint.(Eichler & Zimmerman, 2008)

²⁶⁵⁹ **Cadherins** (calcium dependent **ad**hesion molecules) are type-1 transmembrane proteins that are involved in cell-cell adhesion and they require calcium ions in order to function.

²⁶⁶⁰ In a twin study, Hoekstra ea (2009) found that extreme autistic traits are substantially genetically independent of intellectual disability.

Some findings in autism (roughly as published)²⁶⁶¹

Reduced Purkinje cell counts in the cerebellum

Normal and abnormal brainstem auditory evoked potentials to high intensity stimuli in younger and older cases respectively
Abnormal brainstem auditory evoked responses using an ipsilateral masking procedure may delineate most autistics from most intellectually disabled children - further work is required on reports of prolongation of early brain auditory-evoked response inter-peak latencies in autism

Non-replicated report of hypoplasia of the cerebellar vermis in both retarded and non-retarded patients with autism on MRI

MRI: a number of cortical defects (e.g. macrogyria and cortical clefts) in studies with small numbers - may relate to defective neuronal migration during foetal life

MRI (males): brain enlargement due to increased brain tissue volume (increased grey matter) and enlarged ventricles

Enlargement of hippocampus in some but not all MRI studies (Rojas ea, 2004)

MRI: corpus callosum size may be relatively small in autism

MRI study from birth through age 2 years: generalised enlargement of cortical (gray and white matter) but not cerebellar volumes at 2 years in autism, the onset of enlargement likely being during the latter part of the first year of postnatal life (Hazlett ea, 2005)

Some MRI results have been entirely negative, as has some SPET (SPECT) studies, although there is a suggestion that metabolic maturation of the frontal cortex may be delayed

MRI on MZ twins: white matter growth may be reduced or delayed (Kates ea, 2004)

PET study of autistic children listening to speech-like sounds found diminished activation in left speech-related areas,(Boddaert ea, 2004) confirming previous results obtained in adults (Boddaert ea, 2003) Combined PET/MRI in high functioning autism: smaller and relatively inactivated right anterior cingulate gyrus areas relative to controls

MRI (Palmen ea, 2005): no differences between non-affected relatives and healthy controls

Non-specific hyperserotoninaemia in one-third of cases

Although cholinergic enzyme markers are normal in autism, many nicotinic (high-affinity) and moderate muscarinic M1 receptor measures in the cerebral cortex are lower than normal

Brain-derived neurotrophic factor level in basal forebrain is higher than normal

MRI: larger right amygdala at 3-4 years associated with more severe clinical course and worse outcome at 6 years of age (Munson ea, 2006)

Initial support for genotype-specific phenotypes for serotonin transporter gene promotor in autism (Brune ea, 2006)

MRI: autistic people with small amygdala slowest to distinguish emotional from neutral expression and show least eye region fixation (Nacewicz ea, 2006)

MRI: women with autistic spectrum have similar brain abnormalities to men (Craig ea, 2007)

MRI: adult autistic spectrum disorder (Asperger's, autism, and pervasive developmental disorder not otherwise specified) associated with small cerebellum and increase in peripheral CSF.(Hallahan ea, 2009)

MRI: adults with autism spectrum disorder with/without psychosis v healthy controls – all patients had decreased grey matter bilaterally in temporal lobes and cerebellum and increased grey matter in striatum; those with psychosis had reduced grey matter in frontal and occipital areas; psychosis is associated with reduced grey matter in of right insular cortex and bilaterally in cerebellum extending into fusiform and lingual gyri.(Toal ea, 2009)

MRI: amygdala volume was increased relative to control subjects in autism at age 2 years with no further relative increase at 4 years and amygdala volume was associated with joint attention that requires focusing on eye area of the face.(Mosconi ea, 2009a)

MRI: MZ twins discordant for autism (one with narrowly defined autistic deficits, the other with varying levels of such deficits – ages 5-14 years) compared with normal singletons: alterations in PFC, corpus callosum, and posterior vermis found in autistic children and these vary in degree with severity of autism phenotype (Mitchell ea, 2009)

MRI: In adults with autism spectrum conditions: specific local increase in cortical thickness of the fusiform gyrus and associated impairment of face processing; anatomical covariance between amygdala volume and increase in fusiform gyrus local thickness was significantly smaller in adults with autism spectrum conditions than in healthy controls (Dziobek ea, 2010)

MRI-PET: autism spectrum associated with larger right caudate and reversal of expected left>right hemispheric asymmetry, and lower relative glucose metabolic rates bilaterally in ventral caudate, putamen, and thalamus (Haznedar ea, 2006)fMRI study (Allen & Courchesne, 2003): compared to healthy controls, autistic patients showed significantly greater cerebellar motor activation (pressing a button v rest condition) and significantly less cerebellar attention (pressing a button on seeing a target stimulus v passive looking) activation

fMRI study(Müller ea, 2003): male autistics activated different brain areas from controls when doing finger press movements prompted by visually presented repeating 6-digit sequences

Minor obstetric problems in autism may reflect a genetically abnormal foetus (Le Couteur, 1993)

fMRI: possible amygdala hyperarousal in autism spectrum disorders in response to socially relevant stimuli; sustained amygdala arousal might contribute to social deficits (Kleinmans ea, 2009)

MRI: right-handed, non-mentally retarded boys with autism had decreased brainstem gray matter volume relative to controls (Jou ea, 2009)

fMRI: low levels of autistic traits are found when much of the anterior mid-insula had positive connectivity with the pregenual anterior cingulate cortex²⁶⁶²; increased levels of autistic traits are associated with negative connectivity between these 2 regions (Di Martino ea, 2009)

PET: high-functioning autism (20 men) has widespread decreased 5-HT transporter binding in brain (in the thalamus this correlated with obsessional symptoms/behaviour); dopamine transporter binding is increased in OFPFC and this inversely correlated with 5-HT transporter binding; the authors admitted that their sample was not typical of all adults in the community (Nakamura ea, 2010)

²⁶⁶¹ Neuroimaging results are difficult to interpret overall and there remains a danger of finding what is being sought!(Deb & Thompson, 1998)

²⁶⁶² The pregenual anterior cingulate cortex is important is important for 'theory of mind'.

MRS: autism spectrum associated with increased concentration of glutamate/glutamine and creatine/phosphocreatine in amygdala-hippocampal region but not in parietal region (Page ea, 2006)

Disturbed control of voluntary behaviour in autism spectrum disorders as reflected in repetitive behaviours may be due to alterations in frontostriatal systems as indicated by failures to inhibit prepotent responses (increased rates of prosaccade errors) on an antisaccade task; prosaccade errors were associated with the level of higher-order (compulsions, preoccupations, etc) but not sensorimotor behaviours (Mosconi ea, 2009b)

There is an increased incidence of fragile X, PKU, epiloia, and neurofibromatosis.

Clinical features include aloofness²⁶⁶³, gaze avoidance, attachment to unusual objects like spoons, obsession with maintaining the same routines and environment, catastrophic reactions, finger flicking close to eyes, flapping of hands, jumping, grimacing, turning, walking on toes, and mutism. There are also meaningless speech, immature speech, lacking in gestures, poor comprehension, lack of sense of humour, rage reactions, self-mutilation, incongruity of affect, aimlessness, and lack of involvement in childhood pastimes. I-you pronominal reversal and inappropriate echoing is often found in those who achieve speech. The 'autistic triad' consists of autistic aloneness, speech and language disorder, and an obsessive desire for sameness. Neuropsychologists report sequencing, abstraction and symbolic meaning deficits, and impaired ability to make socio-emotional discriminations and to use socio-emotional cues.(Bölte & Poustka, 2003) Socially and intellectually the prognosis is poor in most cases but a minority does reasonably well. Three good prognostic pointers are significant improvement by age 7 years, IQ of at least 60, and adequate speech development by 5 years. The speed with which other symptoms are discarded is a useful indicator of future adjustment. Autistic patients visually fixate on mouths and objects rather than the eyes of other people. Better and worse social adjustments are associated with fixation on mouths and objects respectively. The shorter the time spent fixated on eyes the stronger the likelihood of autism.(Klin ea, 2002) There is no specific treatment, therapies varying from vitamins to stimulants. Parents need reassurance, support and guidance. Tranquillisers and hypnotics may be needed, but there may be idiosyncratic reactions and non-responsiveness. Secretin (a gut hormone normally given by IV infusion but which can be administered transdermally or sublingually) received huge publicity in 1999 in the US as a dramatic treatment for autism. A small percentage of cases appeared to disimprove when given secretin and its usefulness was not confirmed in placebo-controlled studies.(Owley ea, 2001; Roberts ea, 2001) Efficacy of D-cycloserine therapy for social withdrawal is supported by a pilot study.(Posey ea, 2004) The main intervention comes under the heading of general education. Parents must be part of the treatment team. Behavioural approaches are of adjunctive status only and the French practice of 'packing' autistic children in cold wet sheets for long periods is highly controversial!(Spinney, 2007) Parents may deliberately intrude into the child's life in order to increase social interaction. Stimulants are not indicated for hyperactivity because they do not work and they may make it worse. Risperidone may reduce tantrums, aggression, and self-injurious behaviour,(Research Units on Pediatric Psychopharmacology Autism Network, 2002, 2005) at least while it is being taken. Similarly, risperidone was found to improve restricted, repetitive, and stereotyped behaviours and interests in autistic children, but to be ineffective in changing deficits in social interaction and communication.(McDougle ea, 2005) King ea (2009) found a lack of efficacy of citalopram in the treatment of repetitive behaviours²⁶⁶⁴ in children and adolescents with autistic spectrum disorders. Differential diagnosis includes constitutional shyness, fear (e.g. CSA), normal acting strange phase (6-7 months of age), schizoid personality disorder, simple schizophrenia, deafness (can be fluctuant with secretory otitis media), upset over family problems, depression, specific language impairment, brain damage, intellectual disability, Asperger's syndrome, OCD, and elective mutism. Schizophrenia is no more common in Kanner's syndrome than in the general population. In other words, these children do not grow up to be schizophrenic. Schizophrenia should not be diagnosed in patients with autistic disorder unless there is independent evidence (delusions and hallucinations) for it.(Nasrallah & Smeltzer, 2002, p. 41)

²⁶⁶³ Not all cases conform to the classic *aloof* stereotype. *Passive* cases will accept the approaches of other people, albeit passively or with level of contentment, and will approach others to have needs attended to. Finally, an *active-but-odd* group do make spontaneous if one-sided and persistent approaches.(McKenna, 2007, p. 408)

²⁶⁶⁴ These include stereotyped movements, inflexible routines, repetitive play, and perseverative speech.

Kufs' disease²⁶⁶⁵

Ceroid lipofuscinosis²⁶⁶⁶ in adults; sporadic or familial (recessive or dominant); with lipofuscin deposition in nerve cells, myoclonus, dementia, and cerebellar and extrapyramidal signs

Metachromatic²⁶⁶⁷ **leucodystrophy (O'Shea, 2010a)**

Autosomal recessive (multiple mutations described on chromosome 22q)

Decreased aryl sulphatase A levels in lymphocytes

A sphingolipid (sulfatide) accumulates in tissues

Diffuse loss of CNS myelin

Affected adult may develop cerebellar and long tract signs, neuropathy, behaviour disorders, personality change, psychoses, and progressive dementia

Mercury poisoning²⁶⁶⁸

Most medical devices containing mercury have been removed from circulation

In severe cases delirium proceeds to coma

Milder cases are tired, irritable, insomniac, and wish to be left alone, so-called 'erythrim'

Other complications include coarse tremor ('hatter's shakes'), sensorimotor neuropathy, nephrotic syndrome, uraemia, ptyalism, spongy haemorrhagic stomatitis, loose teeth, weight loss and GIT upset

'Pink disease' (acrodynia) is a childhood disorder, rare today, due to mercury-containing teething powders, nappy powders, ointments or worming formulations: the child is miserable and has skin rashes, muscle weakness and red extremities

SPECT may show hypermetabolism in the posterior cingulate cortex

The clinical picture varies depending on the type of mercury: organic mercury, as from contaminated fish, causes mainly neurological problems (neuropathy, ataxia, visual field defects) whereas inorganic mercury causes 'Mad Hatter's disease', i.e. mainly neuropsychiatric problems (irritability, depression, psychotic states)

Motor Neurone disease (MND, Lou Gehrig's disease, amyotrophic lateral sclerosis²⁶⁶⁹, **ALS)**²⁶⁷⁰

Most cases are sporadic and idiopathic

About 10% of cases run in families

Linkage studies have identified a number of genes, some autosomal dominant, others autosomal recessive

The first gene to be discovered was SOD1 (chromosome 21, autosomal dominant, encodes superoxide dismutase 1), the cause of ALS1

May develop frontal lobe dementia that follows a rapid course

Disturbed emotional responses with inappropriate and uncontrollable laughter and crying²⁶⁷¹

²⁶⁶⁵ Hugo Friedrich Kufs (1871-1955), Leipzig neuropathologist.

²⁶⁶⁶ The **neuronal ceroid lipofuscinoses**, a subgroup of the lysosomal storage disorders, are mostly autosomal recessive disorders. Childhood forms cause intellectual and motor deterioration, blindness, a variety of seizure types, and early death. Dementia is the main feature of the adult forms. The infantile form (Santavuori-Haltia-Hagberg disease) is mainly found in Finland while the late infantile form (Jansky-Bielschowsky disease) commences between 2 and 4 years of age and the juvenile form (Vogt-Spielmeier disease, Batten disease) starts at 5-10 years of age. Kufs' disease starts in adults with progressive myoclonic epilepsy and sparing of the eyes. There are also congenital and a dominantly inherited adult form (Parry disease). For a further introduction see Steinlein.(2008)

²⁶⁶⁷ Metachromatic – chemical looks a different colour depending on wavelength of light.

²⁶⁶⁸ The old saying 'as mad as a hatter' referred originally to a condition developed by hatters who used **mercury** to hold down felt fibres on top hats. During the period 1953-67, a factory on Minamata Bay, Kyushu, Japan, deposited mercury waste into the sea. Many thousands developed different degrees of mercury poisoning ('Minamata disease'), some being fatal. Mercurialism was first reported in New Jersey in 1860 (5 years before Lewis Carroll's 'Alice in Wonderland'). Mercury is found in thermometers and sphygmomanometers (still used in Ireland in 2007: McKeon, 2009), folk cures, botanical preparations, contaminated fish (especially predators), explosives, seed dressings, dental amalgam, and (see pink disease) teething powders. The fetus may be at special risk for developmental reasons when mother consumes contaminated fish. The present author recalls the silver discoloration of gold wedding rings among female physiology staff when he was a student.

²⁶⁶⁹ Whilst in the US amyotrophic lateral sclerosis (ALS) is synonymous with MND, on this side of the Atlantic ALS is, along with progressive muscular atrophy, progressive bulbar and pseudobulbar palsy, and the rare primary lateral sclerosis, but one subtype of MND. However, these subtypes may merge into one another in the later stages of disease progression.

²⁶⁷⁰ The actor David Niven died of MND.

Neuronal degeneration in brainstem

Distressing to patient and family

Diseases causing psychiatric phenomena plus lower motor neurone signs, apart from MND, include HIV and the leucodystrophies

Multiple system atrophy

Idiopathic sporadic condition starting during 40s or 50s and patient dies in about 9 years

Variable atrophy of cerebral cortex, striatum, pontine nuclei, inferior olivary nuclei, and cerebellum

Cytoplasmic inclusions in oligodendroglia

Although mixed forms are commoner (especially with the passage of time), three presentations have been described: striatonigral, olivopontocerebellar²⁶⁷², and Shy-Drager (intermediolateral spinal gray matter involvement causing autonomic symptoms) variants

Suspect this diagnosis when there is Parkinsonism plus autonomic failure, pyramidal signs, vertical gaze palsy, or ataxia

There may be insomnia, diurnal somnolence, REM sleep behaviour disorder

Other problems may include depression, emotional lability, and mild frontal lobe syndrome dysfunction

Variable response to L-DOPA

Myasthenia gravis

Anti-nicotinic acetylcholine receptor antibodies are commonly found in this condition. Early signs include depression, hypochondriasis, hysterical reactions (*and* misdiagnosis of hysteria or feigning), diplopia, ptosis, general weakness (worse at night, if emotional, or during menstruation), difficulty with swallowing and mastication (may need to support jaw), a flattened expression (loss of normal wrinkles +/- a snarl, and inability to smile), and a nasal voice which fades with use. If a nerve is stimulated at 2-10Hz (repetitive stimulation test) action potentials do not vary in normals. In myasthenia gravis the amplitude may fall over successive stimulations²⁶⁷³. An EMG from a single muscle fibre should show stable times between muscle fibres from the same the same muscle unit but in myasthenia gravis the time between firing may vary.

Lithium is contraindicated because it blocks Ach release in therapeutic dosage. Because myasthenia gravis is associated with increased resistance to and slow recovery from depolarising muscle relaxants (e.g. during ECT), a reduction in dosage may be required. Unfortunately, such patients are very sensitive to non-depolarising agents. (Weiner ea, 2001, p. 34)

At least 10% of cases have a thymoma and Mediastinal tomography should be formed to check on thymic status (and to look for bronchogenic carcinoma in cases of Eaton-Lambert syndrome).

Neuroacanthocytosis (choreoacanthocytosis)

An often familial neurological disorder: autosomal recessive (VPS13A gene mutation at 9q21, coding for chorein)

Various psychiatric symptoms e.g. personality change, paranoid delusions, depression, anxiety, and OCD
Chorea, seizures, progressive dementia

Involuntary biting of lips and tongue in a few cases

²⁶⁷¹ **Involuntary emotional expression disorder:** This phenomenon, noted by Hippocrates and Charles Darwin, has been known under many names, e.g. affective/emotional lability, pathological affect, emotionalism, emotional incontinence/dyscontrol, pseudobulbar affect/crying, forced laughter or crying, and involuntary emotional expression disorder. It appears to be caused by disruptions of regulatory/inhibitory mechanisms in the cortico-limbic-subcortico-thalamo-cortico-cerebellar network and may involve 5-HT, dopamine, glutamate, sigma receptor neurotransmitters. Various treatments have been used, such as antidepressants, dopaminergic agents, and combined dextromethorphan-quinidine. (Rabins & Cummings, 2007)

²⁶⁷² T2-weighted scans may show 'hot-cross bun' sign (crossed lines) at base of pons.

²⁶⁷³ In the **Eaton-Lambert syndrome**, amplitude increases progressively over successive stimulations (so-called inverse myasthenia). Anti-nicotinic acetylcholine receptor antibodies are not found. There may be antibodies voltage-regulated calcium channels at the neuromuscular junction. Clinical findings may include proximal atrophy and weakness, ptosis, diplopia, xerostomia, and tendon reflexes that disappear but return when muscular effort is sustained. The syndrome is often (about 2 out of 3 cases) associated with neoplastic disease (e.g. oat-cell) and may precede signs of cancer by a very long period of time. Anticholinesterases are unlikely to be very effective. Steroids, immunosuppressants, 3,4-diaminopyridine, guanidine, and plasma exchange may reduce symptoms.

Spiky projections in red cells (acanthocytes)²⁶⁷⁴

Onset at any age

Organophosphate poisoning

Organophosphates²⁶⁷⁵ inhibit cholinesterase leading to increased availability of acetylcholine (Ach)

Acute exposure causes a cholinergic crisis

Symptoms include tension, anxiety, irritability, restlessness, and headache with high-level exposure

May be weakness, muscle fasciculation, tachycardia, small pupils, lacrimation, sweating, seizures, and coma

Proximal muscle weakness and hyporeflexia may follow later

Chronic low-level exposure associated with increased GHQ scores, reduced attention span and slowed information processing

These problems may persist after removal from exposure

Mood changes and memory problems may persist after an acute cholinergic crisis

Progressive multifocal leucoencephalopathy (PML)

Papovirus (JC, SV-40, etc) infection

Presents as dementia in immunocompromised (e.g. AIDS, Hodgkin's disease, sarcoidosis, leukaemia) individuals

Natalizumab may induce PML

Progressive cerebral destruction with demyelination

Multiple white matter lesions on MRI

Diagnosed by histology and virology of brain tissue

Huge astrocytes with distorted nuclei and abnormal mitotic activity

Inclusions in nuclei of oligodendroglia

Death usually follows after some months

Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)

Dudley Moore (1935-2002), English comedian and actor, was a victim of this disease. In this rare²⁶⁷⁶ idiopathic disorder there is cell loss and gliosis in the basal ganglia, brainstem, and cerebellar nuclei, with relative sparing of cortical neurones. There are neurofibrillary tangles that, unlike in AD, consist of straight tubules. There is depletion of DA in the substantia nigra and basal ganglia and of choline acetyltransferase and glutamic acid decarboxylase in the basal ganglia. MRI may show midbrain atrophy. It commences in the sixth decade of life and continues for 5-10 years until death supervenes. Features include supranuclear paralysis of external ocular muscles²⁶⁷⁷ (especially in the vertical plane – patients have problems looking downward so that they miss steps on the stairs), dysarthria (slurred growling), pseudobulbar palsy²⁶⁷⁸, dystonic trunk and neck rigidity, cognitive dysfunction (extreme slowing of responses, apathy, difficulties recognising similarities, concrete interpretation of proverbs, and apparent memory difficulties²⁶⁷⁹), depression, social avoidance, psychosis, personality change, and labile emotions. There may be dysfunction of the cerebellum and pyramidal tracts. Frequent falling, often backwards, is a common presentation. Unlike Parkinson's disease cases, there is no tremor of the hands and there is a less favourable response to levodopa. Memory difficulties and behaviour/personality may occur in some cases due to fronto-temporal lobar involvement. At the latest stage there is a bedridden patient whose eyes are fixed centrally and all of

²⁶⁷⁴ Found in fresh wet smears of peripheral blood (may be missed if a number of specimens are not taken).

²⁶⁷⁵ Used for agricultural pest control, sheep dipping, as well as chemical warfare (Sarin, VX, etc).

²⁶⁷⁶ Incidence: 1/100,000 of pop.

²⁶⁷⁷ This may give rise to a stare reminiscent of the painting *Mona Lisa*.

²⁶⁷⁸ The full picture of **pseudobulbar palsy** (bilateral upper motor neurone lesion) includes emotional incontinence, difficulty protruding the tongue, dysphagia, dysarthria, and increased gag reflex and jaw jerk. The cause is bilateral interruption of corticobulbar fibres at some point between cortex and pons. Aetiology covers cortical infarction, lacunar infarctions in the sub-cortex, Alzheimer's disease, Binswanger's disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy, MS, head injury, Behçet's disease, amyotrophic lateral sclerosis, and progressive supranuclear palsy. Differential diagnosis of emotional incontinence (no control over laughing which may embarrass patient) include post-CVA emotionalism (congruent emotional display and feelings), inappropriate affect as in schizophrenia (may feel the opposite to the emotional display), and the labile mood of the manic (congruent display of affect and associated emotional feeling).

²⁶⁷⁹ Patients may get the correct answers if given plenty of time.

whose limbs are rigid. Specific tau gene mutations (64 and 68 kDa, as in CBD) have been reported in rare families with a similar syndrome. However, the majority has a negative family history and no single gene has yet been incriminated.

Disseminated candidiasis

Meningitis, vasculitis, abscesses

Occurs in immunocompromised patients

Lethargy, confusion, drowsiness, headache

There may be psychiatric symptoms

No evidence for occult *Candida* infection causing various physical and psychological problems

Cat-scratch fever

Bartonella henselae infection

Found in children who are bitten/scratched by a cat

Most cases have lymph gland involvement that remits spontaneously

Encephalopathy²⁶⁸⁰: lethargy, seizures, and combativeness

Rocky Mountain spotted fever

Infection with *Rickettsia rickettsii* (transmitted by tick bite)

Pyrexia, malaise, muscle pain, and headache followed by rash (starting at wrists and ankles)

There may be lethargy or delirium

Focal signs are not uncommon

Brucellosis

Acute infection: pyrexia, sweating, and muscle and head pain

Chronic infection (there may be no acute history): depression, fatigue, and various pains

CNS involved in 1 in 20 cases: meningitis, psychosis, cranial nerve involvement

Stammering (stuttering)

There is impaired continuous utterance with a complex, multifactorial, heterogeneous aetiology.

Developmental cases affect 1% of adults. Genomewide scans have suggested linkage at many chromosomal sites, e.g. on 12q in Pakistani families.(see Fisher, 2010) It is made worse by stress and interferes with psychological maturation. Scanning shows exaggerated right hemispheric activity suggesting abnormal motor control.(Breathnach, 2000) There have been a few published case reports of clozapine-induced stuttering.(e.g. Duggal ea, 2002; Lyall ea, 2007)

Stiff-person (stiff-man) syndrome (Moersch-Woltman syndrome)

This rare (affecting the sexes equally and being probably autoimmune in origin²⁶⁸¹) condition was described in 1956. It can start in children under 3 years (espc. infants, who are at risk for sudden infant death) or in adults (usually in 3rd to 5th decades). There are constant painful contractions and spasms of voluntary muscles (twisting and contracting may even fracture bones), especially the back and thighs; it may spread to the arms and neck. It is exacerbated by emotion, sudden noise or movement and alleviated by sleep. Kyphosis and lordosis may occur. Diazepam helps most cases. Other treatment options include

²⁶⁸⁰ Temperature may be only moderately raised.

²⁶⁸¹ Stiff-person syndrome may also be a paraneoplastic syndrome with antibodies against the synaptic protein amphiphysin.

baclofen, phenytoin, clonidine, tizanidine, IV immunoglobulins, physiotherapy, and rehabilitative techniques. Outlook is uncertain.

Sydenham's chorea (St. Vitus' dance)

This starts 1-6 months after the carditis of rheumatic fever. It is uncommon today. Average duration is 2 months.

Sydenham's chorea

Affects children 5-15 years of age

Onset insidious with grimacing, limb movements, etc

Movements can be exaggerated by making child hold a fixed posture, e.g. 'stand to attention' or 'stand on the ball of one foot'

During the illness the patient is listless, irritable, and emotionally labile

Explosive or halting speech may occur

50% have residual minor psychological problems

Obsessive-compulsive symptoms are over-represented.

About a quarter of cases eventually develop rheumatic valvular disease

MRI shows a swollen head of caudate nucleus

At postmortem, and therefore in severe cases, there are extensive microscopic haemorrhages. One-fifth of cases may recur when the patient starts on the contraceptive pill or when they become, usually for the first time, pregnant. Sydenham's chore may be caused by genetic susceptibility to cerebrovascular inflammation triggered by streptococcal infections. It might be related to hyperoestrogenaemia - girls more often than boys get it during puberty, and also, as seen above, there is the connection with the pill and with pregnancy. It is possible that a permanent increase in DA sensitivity occurs. Possible causes of the mental problems during the illness are increased DA sensitivity, exhaustion, and cerebro-vascular inflammation. Post-illness neurotic symptoms are said to be not uncommon. Because this disorder has its onset in childhood, the main psychological changes are behavioural: hyperkinesis, restlessness, emotional lability and, rarely, manic episodes. Treatment is largely symptomatic. The abnormal movements may be controllable with pimozide (Orap).

Systemic (disseminated) lupus erythematosus (SLE)

Small cerebral blood vessels may be affected in SLE, with scattered infarcts and bleeds. There is inflammation, damage, and intimal proliferation. There may be alternating narrowing and dilatation²⁶⁸² of vessels.

SLE onset peaks in women between late teens and early 40s; it is 9 times more common in females than males; and African and Asian ancestry carries increased risk. (D'Cruz ea, 2007) SPECT may show multiple perfusion defects. Oestrogen preparations (e.g. anovulants) may exacerbate SLE and increase the risk of thrombosis. Tests for anti-nuclear antibody (ANA: non-specific but sensitive) and for antibodies to dsDNA (double-stranded DNA) and Sm (Smith) antigen are appropriate investigations. SLE is notorious for the variety of neuropsychiatric guises under which it may present: epilepsy (any type), strokes, peripheral neuropathy, myasthenic syndromes, mild or psychotic affective disorders, dementia (see Sundquist ea, 2008), and uncommonly, transient recurrent hemiplegia. In one study (Thomas and Bresnihan, 1986) of 50 successive patients with SLE presenting to a tertiary referral rheumatology department, the following neuropsychiatric manifestations were noted; total (78%), headache (40% - recurrent, severe, migrainous type), depression (26%), peripheral neuropathy (18%), acute brain syndrome (14%), epilepsy (12%), paresis (10%), cranial nerve palsy (19%), ataxia (6%), chronic brain syndrome (6%), and (N=1) chorea (2%). Ruiz-Irastorza ea (2001) and Mak ea (2009) provide a much longer list of neuropsychiatric manifestations of SLE, of which delirium, anxiety, cognitive dysfunction, mood disorder, and psychosis are of particular relevance to psychiatrists. A number of syndromes associated with involvement of the peripheral nervous system have been reported, e.g. Guillain-Barré syndrome, polyneuropathy, and myasthenia gravis.

²⁶⁸² So-called 'beading': usually associated with vasculitis.

Subacute sclerosing panencephalitis (SSPE)

May follow measles infection or (rarely) after measles vaccination (latter has actually reduced SSPE incidence)

Usually in people under 11 years of age, M > F

High levels of measles antibody in CSF

Paretic curve on Lange's colloidal gold test

Paramyxovirus-like particles seen budding from cytoplasmic inclusions on electron microscopy

Transmissible to other species via intracerebral brain tissue inoculation

Initial distractibility, oppositionality, temper outbursts, and fall off in scholastic performance

Sleepiness and hallucinations, confined to bed by 6 months

Dementia, myoclonus, cortical blindness, chorioretinitis, optic atrophy, quadriplegia and coma

MRI (T₂-weighted) hyperintensity of occipital lobe and subcortical white matter, relative frontal sparing

Bursts of triphasic slow waves on EEG

Death within 12-36 months

Progressive rubella panencephalitis**Affects children exposed to rubella *in utero* and resembles SSPE****Thallium poisoning**

Usually due to ingesting rat/insect poison

Acute cases associated with GIT symptoms, delirium, seizures, painful sensory polyneuropathy, cranial nerve signs (loss of vision, double vision, facial palsy), and alopecia

Chronic ingestion associated with dementia, alopecia, and painful sensorimotor polyneuropathy

Tin poisoning

Can cause delirium and seizures

Trichloroethylene poisoning

Degreasing solvent

Exposure may occur occupationally or due to contamination of drinking/bathing water

Neurotoxicity may be due to trichloroethylene or to its derivative dichloroacetylene

Acute effects include headache, dizziness, nausea, vomiting, confusion and various levels of lowered consciousness

Facial anaesthesia, reduction in taste sense, ptosis/diminished pupillary responsiveness/constricted visual fields, dysarthria, flattened nasolabial folds, encephalopathy, and sensorimotor neuropathy may persist

Chronic exposure leads to anorexia, trigeminal nerve damage, fatigue, irritability, headache, paraesthesiae, dizziness, sleep/memory/concentration problems, sexual dysfunction, and peripheral neuropathy

Children may experience problems with hearing and speech

Tuberculosis

TB meningitis has experienced resurgence because of HIV. Basilar meningitis is usually insidious in onset and causes headache, a low fever, malaise, and delirium, with/without neck stiffness. There may be cranial nerve palsies (III, IV, VI, and VII). Hydrocephalus causes a dramatic clinical deterioration. A tuberculoma presents as a space-occupying lesion, often with seizures. Diabetes insipidus and hypernatraemia may follow hypothalamic involvement. Staining of CSF often misses the causative organism, culture is frequently positive (but takes 8 weeks), and PCR assay may reveal DNA from *M. tuberculosis*. The PPD may be negative in AIDS. MRI shows basilar meningitis²⁶⁸³ and, if present, tuberculomata. The fundus may

²⁶⁸³ Oedema, focal infarcts, exudate in basal cisterns, and hydrocephalus on MRI.

show choroidal tubercles. Early treatment is associated with good recovery but neurologically complicated cases may be left with a variety of sequelae²⁶⁸⁴. Untreated cases die in a state of decerebrate rigidity.

African trypanosomiasis

‘Sleeping sickness’ is transmitted by the tsetse fly. The early stages include, fever, weakness, glandular and skin involvement, with enlargement of liver and spleen. A chronic meningoencephalitis is associated with tremulousness, seizures, hemiplegia, apathy, somnolence, and coma. Psychiatric symptoms (irritability, aggression, apathy, inactivity, and psychosis) may dominate the clinical presentation and lead to psychiatric admission! (Brun ea, 2010)

Typhus fever

This rickettsial, body louse-borne disease damages the endothelium of small vessels with resultant thrombosis and necrosis. Glia, phagocytes and endothelial cells may form nodules. A rash appears on the fifth day. As the fever decreases there may be significant manifestations of CNS involvement: headache, delirium, stupor, coma, hemiplegia, bulbar signs, ataxic gait, optic neuritis, deafness, and meningism. CNS damage may be permanent. The CSF demonstrates increases in lymphocytes and globulin.

Whipple’s disease²⁶⁸⁵

Caused by the bacterium *Tropheryma whippelii*²⁶⁸⁶, the most common manifestations stem from joint and intestine involvement (steatorrhoea, weight loss, abdominal pain). Involvement of the CNS is associated with focal inflammation and necrosis and glial scars in many brain areas. PAS-positive macrophages are found in affected areas. MRI may help to locate lesions. CSF reveals a mild increase in lymphocytes with/without raised protein levels. Other tests include looking for PAS-positive macrophages in jejunum or CSF. There may be dementia, delirium, personality change, supranuclear ophthalmoplegia, hypothalamic syndromes, somnolence, convulsions, ataxia, myoclonus, secondary (to diarrhoea) B12 deficiency, and movement of the eyes when the jaw moves (oculo-masticatory myo-arrhythmia). Treatment is with antibiotics (penicillin or tetracycline +/- steroids).

Wilson’s disease²⁶⁸⁷ (hepatolenticular degeneration)(O’Shea, 2010b)

This autosomal recessive disorder has an incidence of about 1 per million. It results from one of a number of mutations in the ATP7B gene²⁶⁸⁸ on chromosome 13q. Serum caeruloplasmin (hepatically derived copper-containing globulin) is greatly reduced²⁶⁸⁹, liver copper is increased, serum copper concentration is diminished unless fulminant liver failure ensues, urinary copper concentration is increased, and there is failure of incorporation of ⁶⁴Cu (radioactive copper with very short half-life²⁶⁹⁰) into caeruloplasmin. Bronze skin is usually a late manifestation of Wilson’s disease. The Kayser-Fleischer ring²⁶⁹¹ is due to copper deposition in Descemet’s membrane. Sunflower cataracts may be found. There is atrophy and brownish discoloration of the striatum, eventually with cavity formation. Opalski cells are large phagocytic cells found in the brain in Wilson’s disease. Cortical atrophy is mild. Confirmation of diagnosis is by liver biopsy. About 20% either present with psychiatric symptoms or are at least seen by a psychiatrist before definitive diagnosis. (Denning & Berrios, 1989)

²⁶⁸⁴ E.g. various forms of paresis, seizures, blindness, deafness, precocious puberty, diabetes insipidus, sleep problems, and intellectual disability.

²⁶⁸⁵ The American physician George Hoyt Whipple (1878-1976) described this condition in 1907.

²⁶⁸⁶ Rod-shaped as seen by electron microscopy.

²⁶⁸⁷ Samuel Alexander Kinnier Wilson (1874-1937), a London neurologist, described this condition in 1912.

²⁶⁸⁸ This gene encodes a member of the copper-transporting P-type adenosine triphosphatases which exports copper from cells.

²⁶⁸⁹ Numerous mutations have been described and these vary with country of origin.
²⁶⁸⁹ Nearly all plasma copper is bound to caeruloplasmin. Most Wilson’s disease cases have reduced caeruloplasmin synthesis. But, since 5% have a normal serum caeruloplasmin concentration, something else is required for the disorder to manifest itself.

²⁶⁹⁰ Hence a rarely performed test.

²⁶⁹¹ This ring is not only found in (the great majority of cases of) Wilson’s disease. It may also occur in autoimmune hepatitis and in primary biliary cirrhosis.

*Wilson's disease: psychiatric symptoms*²⁶⁹² (Denning & Berrios, 1989)

Aggression, irritability

Disinhibition

Impulsive, incongruous behaviour

Depression

Grimacing or unmoving expression (vacuous expression with open mouth)

Cognitive dysfunction

Psychosis (1%) and drug misuse (both uncommon)

Neurological signs occur in 40% or more of cases (dysarthria, flapping wrist tremor, wing-beating tremor at the shoulders²⁶⁹³, fluctuating limb rigidity, dysarthria, dysphagia, hemiplegia, coma attacks, dystonia, and choreiform movements. The kidneys may be affected as may the joints. Episodic haemolytic anaemia can occur. Cardiomyopathy and cardiac conduction problems have been reported. T2-weighted images may show the 'face of the giant panda sign'.²⁶⁹⁴ Younger age of onset carries a worse prognosis. The main treatments for Wilson's disease are copper chelating (e.g. penicillamine²⁶⁹⁵ and trientine [triethylene tetramine dihydrochloride]) and copper depleting (e.g. zinc and tetrathiomolybdate) drugs. (Lauterbach, 2000) Liver transplantation is sometimes used. Low copper diets are not part of treatment.

Wolfram syndrome (DIDMOAD)

Pathogenesis may involve anti-CNS autoantibodies. The posterior pituitary may be poorly developed or absent on MRI.

Wolfram syndrome

Rare – described in 1938 by Donald J Wolfram MD

Autosomal recessive – mutation in WFS1 gene, chromosome 4

DI - diabetes insipidus

DM - diabetes mellitus

OA - optic atrophy

D - deafness

Other manifestations - ataxia, dysarthria, nystagmus, dysdiadochokinesia, dysphagia, anosmia, and EEG changes

25% - psychiatric problems, e.g. severe episodes of depression, psychosis, organic brain syndrome, and impulsive physical and verbal aggression

Heterozygotes (carriers) also appear prone to significant psychiatric difficulties. A small number have demonstrable CNS changes such as pontocerebellar atrophy.

Amnestic disorders



Kayser-Fleischer ring

²⁶⁹² 195 cases: 60 given psychiatric assessment; half demonstrated psychiatric problems at some stage; one-fifth saw a psychiatrist before definitive diagnosis.

²⁶⁹³ Arms are abducted and elbows are flexed: movements resemble those of a startled bird.

²⁶⁹⁴ There is high signal intensity in tegmentum, hypointense superior colliculus, and preserved signal intensity in lateral pars reticulata of substantia nigra.

²⁶⁹⁵ Penicillamine can cause psychosis and seizures.

These disorders involve impaired memory²⁶⁹⁶. Directly as a result of a general medical disorder or trauma, there is transient (lasting less than one month) or chronic (> 1 month) impaired learning of new information or an inability to recall information that was learned in the past and the memory problem is not confined to a time when the patient is delirious or demented. Such conditions impair the patient's function and are new developments in their lives, i.e. there is a decline from premorbid memory ability. Immediate and remote memory is generally preserved. The patient may be disorientated. Often the patient cannot recall the causative incident. Insight is most often lacking. Confabulation is more common early on in the course of the disorder than in its late stages. The most common cause is probably head injury, although alcohol abuse/thiamine deficiency (dealt with elsewhere) is the classic cause. Known causes are many but include head injury²⁶⁹⁷, seizures, cerebrovascular disease, brain tumours, hypoglycaemia, hypoxia, carbon monoxide (CO) or heavy metal poisoning, Herpes simplex encephalitis, Klüver-Bucy syndrome, acute alcoholic blackout, Wernicke-Korsakoff syndrome, ECT, and drugs (benzodiazepines, barbiturates, MDMA, and intrathecal methotrexate). Acute onset is associated with such causes as cranial injury or CO poisoning. More insidious onset and chronic course is typical of drug abuse, prolonged exposure to toxins, or nutritional deficiency. Transient global amnesia is temporary amnesic syndrome that is discussed below. Most cases of amnesic syndrome are due to bilateral brain lesions involving areas such as thalamic nuclei (dorsomedial and midline), hippocampus, fornix, amygdala, and mammillary bodies. Rare cases are due to extensive left-sided damage. Some causes, such as electroconvulsive therapy, are not accompanied by typical brain lesions. Malingered and factitious cases must be considered in the differential diagnosis.

*Transient global amnesia (TGA)*²⁶⁹⁸

Migraine, epilepsy, Valsalva-induced venous return causing retrograde transmission of high venous pressure to cerebral veins, and reduced blood supply²⁶⁹⁹ to the temporal lobe and diencephalon are among suggested causes. SPECT demonstrated reduced blood flow in temporal and parieto-temporal areas, especially in the left hemisphere.

TGA

Episode of **sudden loss of memory**

Middle-aged/elderly patient suddenly unable to register new information from the senses

May last for a few hours

Memory for earlier events is as normal as ever

Depersonalisation and bewilderment are common

May quizz companions repeatedly

Patient remains alert

Complex functions such as driving do not seem to be adversely affected

Amnesia for events occurring during attack

Normal neurological examination

May be precipitated by neck movements

Benign

Recurrences are uncommon (< 20%)

Mimics: temporal lobe tumour, benzodiazepines +/- alcohol

TGA-like episodes may accompany sexual intercourse, epilepsy, general anaesthesia, migraine, cardiac arrhythmias, myxomatous disease of the mitral valve, and polycythaemia rubra vera.

²⁶⁹⁶ Eric Kandel (Nobel Prize in Medicine in 2000, sharing with Arvid Carlsson and Paul Greengard) was born in Vienna in 1929 and is a contemporary psychiatrist at Columbia University. He studied memory using the gill reflex of the sea snail *Aplysia* and found that the formation of memories occurs at synapses and thereafter different mechanisms and synaptic changes determine whether memory is stored for short or long term use.

²⁶⁹⁷ There is an argument for giving thiamine routinely to the head injured because of the fact that an amnesic syndrome is easy to miss in such circumstances.(Ferguson ea, 1997)

²⁶⁹⁸ Described by Fisher and Adams.(1964)

²⁶⁹⁹ Perhaps due to vertebro-basilar ischaemia.

813 Delirium

Latin *delira* (L. *de lira* out of the row or furrow) meaning ‘off track’, i.e. mad or crazy²⁷⁰⁰

Also known as *acute brain syndrome* or *acute confusional state*

Non-psychiatric medical clinicians were often, until recently, (incorrectly) taught that delirium was not an organic syndrome²⁷⁰¹ (Caplan *et al*, 2008, p. 227)

Aetiological factors are numerous, e.g. Behçet’s syndrome, carbon monoxide, cysticercosis, bacteria, dementing disorders, drugs, drug withdrawal, embolism, endocrine disorders (including diabetes), epilepsy, heat stroke, heavy metals, histoplasmosis, hypertensive encephalopathy, hypoxia, paraneoplastic syndrome, mumps, normal pressure hydrocephalus, sarcoidosis²⁷⁰², trauma, vascular, viruses, vitamin deficiencies, Wilson’s disease, etc

Aetiological factors act on a vulnerable brain to precipitate delirium

Most cases of delirium are multifactorial in origin

Common combination of dementia plus delirium sometimes called *beclouded dementia*²⁷⁰³

Abnormal EEG²⁷⁰⁴ favours diagnosis of delirium but normal recording does not rule it out (APA, 2002, p. 43)

10-30% of medical ill inpatients develop delirium, especially elderly (often prolonged delirium), post-surgical cases²⁷⁰⁵, AIDS (30-40% of hospitalised AIDS cases), terminally ill, burns, dialysis, and CNS lesions

Main causes in HIV patients are medication (e.g. zidovudine, efavirenz²⁷⁰⁶, isoniazid, dapsone, etc), drug use/withdrawal (e.g. alcohol, phencyclidine²⁷⁰⁷), infection (e.g. toxoplasmosis²⁷⁰⁸), neoplasms, and metabolic disorders (e.g. renal failure); anticholinergic drugs (including opioids) may exacerbate delirium

Common in psychiatric patients – iatrogenic, substance misuse, overdose, increased physical morbidity, geriatric depression associated with poor diet and fluid intake, etc

Deafness, poor sight, acute stress, bereavement, depression, brain damage, alcohol/substance dependence, and sensory deprivation are risk factors for delirium

Common in nursing homes – it may become more common outside hospital following shortened hospital stays and an increase in day-surgery (Brown & Boyle, 2002)

²⁷⁰⁰ *Typhus* (Gk) means ‘mist’ or ‘cloud’, a Hippocratic usage to refer to changed mental state in pyrexial states.

²⁷⁰¹ However, ancient physicians appear to have recognised that delirium was a disorder of the brain. They divided it into *phrenitic* (overactive) and *lethargic* (underactive) forms.

²⁷⁰² **Sarcoidosis** may be due to unknown environmental agents interacting with genetically susceptible individuals. The clinical aspects of sarcoidosis of most interest to the psychiatrist are fatigue (often with pyrexia, loss of weight, depression, malaise, and raised C reactive protein), CNS involvement (meningeal inflammation/infiltration, aseptic meningitis, diabetes insipidus, encephalopathy, vasculopathy, seizures, mass effects, and hydrocephalus), and peripheral nervous system effects (cranial nerve palsy [especially VII nerve] and small fibre neuropathy). (Dempsey *et al*, 2009) CNS involvement occurs in about 5% of cases. Psychoneurological symptoms can include apathy, self-neglect, problems with judgement, irritability, hallucinations, schizophrenia-like psychosis, diminished consciousness, and dementia. (Lovestone, 2009, p. 888) Sarcoidosis may be less common in smokers. (Innes & Reid, 2006, pp. 715 & 717)

²⁷⁰³ Perhaps 25% of cases are a combination of delirium and dementia.

²⁷⁰⁴ **EEG:** In mild delirium the EEG shows slowing of the dominant posterior rhythm whereas in severe cases one sees widespread theta and delta rhythms. Severe toxic or metabolic delirium may have triphasic waves instead of diffuse slowing. Withdrawal from alcohol and other sedatives is characterised by low voltage, fast activity. Structural problems are suggested by periodic lateralised epileptiform discharges. Uncommonly, one may diagnose non-convulsive status epilepticus.

²⁷⁰⁵ Especially cardiectomy, hip surgery, or transplantation.

²⁷⁰⁶ Efavirenz can also cause depression, insomnia, vivid dreaming, dizziness, and poor concentration. Such side effects usually resolve by one month and **usually** do not require discontinuation. *Efavirenz can give a false-positive cannabinoid test.*

²⁷⁰⁷ **Phencyclidine** intoxication is associated with ataxia, dysarthria, nystagmus, reduced pain responsiveness, altered body image, agitation, and assaultive tendencies.

²⁷⁰⁸ **Toxoplasmosis**, less common since the introduction of HAART, represents reactivated latent infection with the intracellular protozoan *Toxoplasma gondii*. There is acute meningoencephalitis, diffuse or focal. After a period of lethargy, there may be headache, confusion, and focal neurological signs. Neuroimaging usually shows many ring-enhancing basal ganglia and grey/white matter junction lesions. Pathologically there are scattered abscesses with encysted parasites. Thrombosis leads to necrosis. Treatment is with combined pyrimethamine and sulfadiazine.

Cryptococcosis (*Cryptococcus neoformans*), a fungus, may cause granulomatous meningitis with a thick basal exudate. Features may include malaise, headache, meningism, confusion, changed behaviour, raised intracranial pressure, focal neurological signs, and fungus stained with India ink or presence of cryptococcal antigen in the CSF.

The ascending reticular activating system²⁷⁰⁹ (RAS) of the mesencephalon is responsible for maintaining an activated cerebral cortex and its blood supply is peculiarly open to insult from any significant rise in CSF pressure. It is uncommon for this system to be the site of a primary disorder, but it is often affected by systemic disorders.

Functions of reticular activating system

- Arousal
- Balance
- Control of heart and breathing
- Control of conjugate eye movement

Reactions to organic cerebral insult vary between individuals. Whilst not backed by research evidence (Lipowski, 1980), it is clinically observable that some people weather severe physical insults with equanimity and others 'give in' and become confused.

Most confusional states result from the interaction of three main factors:

1. *Unrecognised complications of a primary condition*, such as pneumonia²⁷¹⁰ arising during detoxification from alcohol
2. *Drug therapy and drug interactions*, such as barbiturates in porphyria
3. *The psychological status of the patient* (related to current emotional expectation and past experience)

Predisposing/precipitating factors in delirium (Hogg, 2008)

Older age, male sex

Dementia²⁷¹¹

Sleep deprivation

Severe illness

Admission for fracture, hospital admission,

Dehydration, malnutrition, reduced mobility

Poor vision/hearing

Polypharmacy (including over-the-counter), anticholinergic load, general anaesthesia (vs spinal anaesthesia)

Use of physical restraints²⁷¹², urinary catheter²⁷¹³

Risk factors for postoperative delirium (Fricchione ea, 2008)

Pre-surgery – old age, dementia, smoking, poor functional status, abnormal electrolytes or glucose levels, and albumin of 4 g/dl or less

During surgery – blood loss, fluid infusion requirements, vascular²⁷¹⁴ surgery

Post-surgery – haematocrit > 30%, multiple blood transfusions, abnormal electrolytes or glucose levels, and albumin of 3 g/dl or less

Psychiatrists should resist any tendency of non-psychiatric physicians to view delirium as a primarily psychiatric concern (APA, 2002, p. 47) and should not agree to the transfer of a delirious patient to a psychiatric ward.

Impaired ability to draw a clock-face may be a useful predictor of postoperative delirium.

Delirium must be distinguished from depression, dementia (especially Lewy body), and mania.

²⁷⁰⁹ The RAS bilaterally projects to the thalami to regulate alertness. Inputs to the RAS from neocortex and limbic system control attention. Acetylcholine is the main RAS neurotransmitter.

²⁷¹⁰ Most people who have dementia of any type will die from bronchopneumonia or from pulmonary embolism.

²⁷¹¹ About one-quarter of older people with delirium have an underlying dementia.

²⁷¹² Other risks associated with restraints are choking, decubitus ulceration, and other consequences of immobilisation.

²⁷¹³ A catheter not only provides a route/nidus for infection, it also reduces mobility.

²⁷¹⁴ E.g. CABG or repair of abdominal aortic aneurysm.

Anything interfering with concentration or perception may precipitate a confusional state, e.g. shadows, dim light, frequent staff changes, inadequate or incorrect drug usage, and admission to hospital. Quite simple things such as constipation, moving shadows, dark corners, poor illumination, dehydration, or urinary retention or infection may precipitate delirium. Drug-induced delirious states may confound the unwary physician. These may aggravate underlying brain damage.

Examples of drugs reported to have caused delirium (incomplete)

ACTH

Antibiotics – e.g. aminoglycosides, gentamicin, isoniazid, metronidazole, sulphonamides, tetracyclines, vancomycin, etc

Anti-epileptics – phenytoin, carbamazepine, vigabatrin, valproate, clonazepam

Antihypertensives – captopril, clonidine, methyldopa, reserpine

Anticholinergics – atropine, benztropine, benzhexol, diphenhydramine, scopolamine, antipsychotics, TCAs, etc

Antiarrhythmics – disopyramide, lidocaine, mexiletine, procainamide, quinidine, etc

Anti-ulcer drugs – cimetidine, ranitidine

Antivirals – acyclovir, interferon, etc

Beta-blockers – propranolol, etc

Central dopamine agonists – amantadine, bromocriptine, L-DOPA, selegiline

Chlorpropamide

Clozapine

Contrast media - metrizamide

Corticosteroids

Digitalis, theophylline

Disulfiram

Diuretics - acetazolamide

Ergotamine

Immunosuppressants – aminogluthethamide, chlorambucil, 5-fluorouracil, tamoxifen, vinblastine, etc

Ketamine

Lithium

MAOIs – phenelzine, procarbazine, etc

Mefloquine

NSAIDs – ibuprofen, indomethacin, etc

Opiate analgesics²⁷¹⁵ – pethidine, pentazocine, etc

Sedative-hypnotics – baclofen, barbiturates, benzodiazepines, Z-drugs

Sympathomimetics – amphetamine, aminophylline, cocaine, ephedrine, phenylephrine, phenylpropanolamine

A history of excessive drinking should always be sought on admission. Industrial poisons like dichlorodiphenyl trichlorethane (DDT) or trichloroethylene (Q.V.) can cause delirium.

The classical understanding of neurotransmitter malfunction in delirium is that DA activity is increased and Ach activity is reduced. DA may act via its regulatory role in Ach release. Cytokines, including interferon, may contribute by increasing blood-brain barrier permeability and influencing neurotransmission. Chronic stress caused by trauma or illness activates the sympathetic nervous system and HPA axis with increase in cytokine and cortisol levels. (see O’Keeffe & Devlin, 1994) Chronic high cortisol levels had deleterious effects on 5-HT_{1A} receptors in the hippocampus that may also contribute to delirium. (Inouye, 2006)

One theory of the perceptual abnormalities of delirium is the escape of dream material into the waking state. Students undergoing sensory deprivation experienced frightening hallucinations similar to those seen in delirium tremens (DTs).

Complications of encephalitis

Prolonged anxiety and depression

Dementia

Personality change

Epilepsy

Behaviour disorder in children

Acute schizophrenia-like psychosis

²⁷¹⁵ Since pethidine can cause delirium and seizures morphine is safer (unless there is renal failure).

Presentations of delirium

Hyperactive ('agitated', 'hyperalert')

Quiet ('lethargic', 'hypoactive', 'hypoalert')

'Mixed' (alternating hyperactivity and hypoactivity²⁷¹⁶)

Mixed delirium is the most common presentation. (Liptzin & Levkoff, 1992) Quiet (hypoactive) cases²⁷¹⁷ of delirium are often overlooked or misdiagnosed as depressed; the patient may drift into sleep during a conversation.

Consciousness is impaired in delirium. The level of consciousness varies over time, often closely related to variations in pain, sedation, or the discernibility of the environment. It may be subtle or profound. The patient has rational periods, especially when spoken to. There may be reduced awareness of the environment, a diminished capacity to attend to specific issues or to shift attention appropriately from one matter to another, and distractibility.

Fear may be marked (and relatives may be distressed). Mood is usually labile. Temporal disorientation is an early feature. Later on there is global disorientation. Confabulation²⁷¹⁸ may occur, as may dysmnnesia. Restlessness usually commences at night (*sundowning*). Insomnia by night, sleep reversal with fitful daytime naps, and agitation are frequently encountered. Violent behaviour should be met with enough attendants to restrain the patient safely. The patient should be spoken to in calm, reassuring tones. The patient's mental life is full, unlike the impoverished cerebration of the demented. Personality or other psychiatric problems may become exaggerated. Hallucinations are usually visual or visual plus auditory. Seizures may cause or complicate delirium.

Double orientation

Person appears to reside in two worlds simultaneously, e.g. recognising a nurse for what she is while at same time believing, wrongly, her to be his daughter

Where appropriate, before prescribing medication one should attempt non-pharmacological interventions such as changing the environment or employing verbal and non-verbal de-escalation. (Young ea, 2010)

Preventing delirium (Young & Inouye, 2007)

Orient the patient

Activate the patient

Good nutrition and hydration

Non-drug management of insomnia and anxiety

Spectacles or hearing aid

Treat pain

Early discharge to home rehabilitation service

Low doses²⁷¹⁹ of high potency antipsychotic drugs like haloperidol may calm the patient – oral doses need to be 1.5 times the IM dose for equal effect. IV haloperidol (usually) cause fewer EPS than when administered by other routes (APA, 2002, p. 36; Fricchione ea, 2008) and it does not interfere with dopamine's effect of increasing blood flow to the kidney. Atypical antipsychotic drugs are increasingly used in the management of delirium: olanzapine, risperidone, and quetiapine cause less EPS than does haloperidol; and quetiapine may cause sedation. The use of antipsychotic drugs should be reassessed if the

²⁷¹⁶ Shifts between overactivity and apathy may occur rapidly.

²⁷¹⁷ 'Dumb rabies' refers to animals or humans with rabies who are listless and immobile instead of raving or 'rabid'.

²⁷¹⁸ There is evidence for confabulation in schizophrenia where it tends to be associated with thought disorder and perhaps with impaired semantic memory. (Lorente-Rovira ea, 2007)

²⁷¹⁹ Excessive dosing is all too common. (Hally & Cooney, 2005) Recommended doses of haloperidol in delirium are 1-2 mg/2-4 hours as required, further dose changes depending on achieving the desired effect. The stabilised patient can be switched to twice-daily dosing or night-time only dosing. Doses can be tapered gradually whilst clinical status is monitored. HIV/AIDS patients should receive very low doses of haloperidol or be prescribed an atypical antipsychotic.

QTc interval extends beyond 450 msec or more than 25% above baseline. Anticholinergic drugs²⁷²⁰ can exacerbate confusion. Chlorpromazine is probably as effective as haloperidol but may adversely affect cognitive status due to its anticholinergic actions. Physostigmine²⁷²¹ can be employed for anticholinergic delirium but it can cause GIT upset, bradycardia, hypotension, cardiac arrhythmias, or seizures. If it is essential to employ a BZD (e.g. to lower the dose of an antipsychotic as when attempting to minimise EPS from IV haloperidol²⁷²²) then low doses of short-acting drugs like lorazepam should be picked. Lorazepam may negatively impact on cognition. Haloperidol on its own is more effective than Lorazepam monotherapy. Mianserin, which is sedative, is often used for delirium in Japan²⁷²³, especially for hyperactive cases and where the symptoms are worse at night. (Someya ea, 2001) Methylphenidate (for hypoactive delirium) and trazodone have also been used to treat delirium. Cholinesterase inhibitors have also been employed, e.g. for delirium on a background of dementia. (Wengel ea, 1998)

ECT has been used successfully to treat delirium due to a wide variety of primary conditions, varying from neuroleptics malignant syndrome to delirium tremens and pernicious anaemia. (Delay & Maillard, 1945; Krystal & Coffey, 1997) Such use should be a rare event.

Apart from alcohol and sedative withdrawal states, BZDs are not primary treatments for delirium. Many delirious patients recover, although there is some evidence that new and permanent cognitive damage may follow delirium. (Bourgeois ea, 2008, p. 304, 317) Possible outcomes of delirium are complete resolution, gradual resolution, or the unearthing or induction of permanent cognitive dysfunction. Resolution of delirium commonly follows some time *after* recovery from the underlying somatic condition, i.e. there is usually a time lag. Mortality is raised commensurate with the severity of the precipitating disorder: 15% die and 4 out of 10 are in institutional care after 6 months.

When patients recover they may need much reassurance and explanation. Pharmacological treatment should continue until there is full resolution of delirium. (Meagher & Leonard)

Mild cognitive impairment²⁷²⁴ (MCI)

MCI illustrates the common absence of clear boundaries in Nature. (Widiger & Mullins-Sweatt, 2007, p. 7) The numbers affected depends on the diagnostic criteria²⁷²⁵ applied. (Busse ea, 2003) There is a variable recall ability of which the patient is aware and for which he may be profuse in his apologies. Names are forgotten, correct words are difficult to bring to mind, items are misplaced, concentration is poor, and complex problems present exceptional challenges. No other cognitive defects are found. Psychiatric symptoms may account for memory complaints²⁷²⁶ (Jorm ea, 2004). Although the risk is real (Jessen ea,

²⁷²⁰ E.g. chlorpromazine, thioridazine, clozapine, ranitidine, codeine, dipyrindamole, warfarin, isosorbide, theophylline, nifedipine, digoxin, pethidine, fentanyl, diphenhydramine, carbamazepine, and prednisolone. Prolonged pethidine (meperidine) use may lead to accumulation of nor-meperidine (half-life 30 hours) which is toxic and can cause psychosis, anxiety myoclonus, and seizures; also, pethidine is contraindicated in combination with MAOIs.

²⁷²¹ IV physostigmine has a short duration of action. Some clinicians give IV glycopyrrolate, which does not cross blood-brain barrier, beforehand to block peripheral cholinergic effects of physostigmine.

²⁷²² E.g. haloperidol 3 mg and Lorazepam 0.5 mg IV as starting doses.

²⁷²³ Japanese insurance does not cover use of haloperidol.

²⁷²⁴ **Mild cognitive impairment (MCI)**, benign senescent forgetfulness, benign memory loss, ageing-associated (or age-related) cognitive decline, or age-associated memory impairment: a common condition, described by V A Krall in 1958. One definition of MCI is that cognitive problems are greater than what is expected for chronological impairment which means age-inappropriate cognitive impairment rather than 'age-associated memory impairment'. We know that memory becomes less efficient with advancing age but this 'age-appropriate memory decline/impairment' does not interfere *significantly* (where is the cut-off?) with functioning, either socially or in work, and activities of daily living (ADLs) are carried out about as well as before (arthritis, deafness, poor sight, and respiratory and other organ dysfunction and so on being factored in).

²⁷²⁵ One set of criteria for MCI (Petersen ea, 2001) cognitive complaints (most often, but not confined to, poor memory), cognitive screening (e.g. MMSE) gives overall results that lie within the normal range, memory testing results are 1.5 standard deviations below norms for the patient's chronological age, ADLs are carried out reasonably well, and (to avoid satisfying DSM criteria for a dementing disorder) there is insufficient impairment of social/occupational activity.

²⁷²⁶ In a population-based study (Geda ea, 2008) the most distinguishing features between people with people with mild cognitive impairment (MCI) and those with normal cognition were apathy, agitation, anxiety, irritability, and depression. Non-psychotic symptoms affected half of people and a quarter of those with normal cognition. Psychotic symptoms were rare. Older community-dwelling people who feel that they have a greater *purpose in life* have been noted to have reduced risk of progression to MCI and AD and a slower rate of cognitive decline. (Boyle ea, 2010) In older Americans living in the community (Wilson ea, 2010) measured cognitive status every three years; at the start of the study 614 had no cognitive impairment, 395 had MCI, and 149 had AD (mostly mild); the annual decline in cognitive function on follow-up (mean = 5.5 years, SD = 2.5) was lowest in the non-affected group, at least twice as high in the MCI group, and more than fourfold in the AD group; and there was no reliable effect of age, sex, or age.

2010), only close follow up can tell which case progresses to a full dementia. However a thyroid screen is prudent, other tests being dictated by clinical findings²⁷²⁷. Different studies suggest different risks for dementia and current cognitive screening instruments do not allow us to confidently prognosticate about the future progress of MCI in individual cases.(Lonie ea, 2009, 2010) As pointed out by Roose and Devanand (1999, p. 5) subjects recruited from newspaper advertisements fair much better than people who approach a professional with cognitive complaints. A 6-year neuropsychological community study of over-75s (Busse ea, 2006) found that 60-65% of people with MCI developed clinical dementia during life, most cases doing so within the first 18 months. In contrast, Mitchell and Shiri-Feshki (2009), in a meta-analysis of 41 studies, found a progression rate of only 10% and 5% per year in high- and low-risk groups respectively, and only 20-40% developed dementia after extended follow-up. MCI is basically a diagnosis by exclusion²⁷²⁸ (Ancelin ea, 2006) and follow up. According to Small ea, (2006) who employed FDDNP-PET, binding of FDDNP²⁷²⁹ is highest in Alzheimer's disease, lower in MCI, and least in normal controls. Tau and Abeta42 levels in CSF were reported as strongly predicting Alzheimer's disease (AD) in patients with MCI.(Hansson ea, 2006) Levels and activity of beta-secretase (BACE1) are elevated in the CSF in sporadic AD and in MCI relative controls.(Zhong ea, 2007) The same group²⁷³⁰ looked at the CSF of APOE ϵ 4 carriers and non-carriers and found that APOE ϵ 4 was associated with elevations of BACE1 in both AD and MCI. Levels of Abeta (1-42) were decreased in APOE ϵ 4 carriers in MCI but not AD. BACE1 may detect in vivo changes in amyloidogenic processing potentially modified by APOE genotype. The combination of APOE ϵ 4 status and depression in elderly men (women not included in study) may increase the risk for dementia.(Irie ea, 2008)

Dutch research (van Exel ea, 2009) looked at heritable traits in middle age that contribute to (late-onset) AD. More offspring of parents with AD carried APOE ϵ 4 than those lacking a parental history; the former also had higher systolic and diastolic blood pressures and lower ankle brachial indices and they also had higher levels of IL-1 β , IL-1 β to IL-1ra ratio, TNF α , IL-6 and interferon γ .

In a meta-analysis of CSF and MRI biomarkers, Schmand ea (2010) found that memory impairment was a more accurate predictor of early AD than MRI evidence atrophy of the medial temporal lobe; CSF tau and beta-amyloid were as predictive as memory impairment; but studies of longer duration are needed for CSF markers.

Galantamine (Q.V.) is contraindicated in MCI.

Dementia

Both delirium and dementia are clinical statements. Whilst delirium is characterised by clouding of consciousness, dementia (chronic brain syndrome) is typically but not invariably an irreversible deterioration in cortical functioning. One definition is that dementia is an acquired, global disorder with intellectual deterioration, memory impairment and personality disorganisation in the presence of unimpaired consciousness. An alternative definition of dementia is that it is an acquired global impairment of memory, intelligence and personality skills, commonly progressive, and with no impairment of consciousness. Dementia usually develops gradually but it may be noticed for the first time following an exacerbation caused by a change in social circumstances or an intercurrent illness. Six years after Pick described his disease Binswanger²⁷³¹ introduced the concept of 'presenile dementia'.

According to Kay and Tasman (2006, p. 365), the cost of care provision for demented people in the US was over \$100 billion each year, amounting to one-tenth of total health care expenditure, and the average annual

²⁷²⁷ An example would be B12 level in chronic alcoholism with liver or peripheral nerve damage.

²⁷²⁸ Depression, dementia, high anticholinergic load, etc.

²⁷²⁹ A molecule that binds to plaques and tangles in vitro.

²⁷³⁰ The group includes Prof Harald Hampel of Trinity College Dublin.

²⁷³¹ The Swiss psychiatrist-neurologist Otto Ludwig Binswanger (1852-1929) was professor of psychology at Jena, a pupil of Meynert and Westphal, and physician to the German philosopher Friedrich Nietzsche.

cost per family was \$18,000 in 1990. Estimated cost of dementia in community setting in the UK (Stewart, 2008) is £14,540, £20,355, and £28,527/person/year for mild, moderate, and severe cases respectively²⁷³². Total cost per inhabitant of Ireland of dementia is €79.(McHugh ea, 2007)

'Presenile' simply means less than 65 years of age
About 15% of the population is over 65 (i.e. 'senile'); 10% of these will have some degree of dementia;
about 40% of that 10% will have severe dementia
About 80% of dementers are still at home

A population-based cross-sectional study in Rotterdam (Ott ea, 1995) found an overall prevalence of dementia of 6.3%²⁷³³. AD accounted for 72% and it also accounted for the pronounced increase in dementia with increasing age. All other causes showed less contribution to an association with increasing age. Vascular dementia, Parkinson's disease-associated dementia and others accounted for 16%, 6% and 5% of cases of dementia²⁷³⁴. A substantially higher prevalence of dementia was found in subjects with a low educational level²⁷³⁵. A study of Bavarian nuns²⁷³⁶ found a strong association of low education and occupational attainment with dementia.(Bickel & Kurz, 2009) It has been suggested that education may improve brain reserve by promoting neuronal branching. Alternatively, early dementia might be 'hidden' by superior verbal skills, e.g. high plaque levels on PET scans using [¹¹C]PiB²⁷³⁷ were associated with better cognitive performance in people with higher educational levels.(Roe ea, 2008) An international consensus of experts (Ferri ea, 2005) concluded that there existed 24.3 million people with dementia world-wide; 4.6 million new cases annually; the numbers of cases will double every 20 years; the majority of cases are in the developed world, but the rate of increase may be higher in some developing parts of east and south Asia. The Barberger-Gateau ea (2002) study that showed a protective effect of fish²⁷³⁸ and seafood against developing dementia was contaminated by the finding that higher education was associated with eating such foods. Interestingly, they found no significant association between eating meat and dementia. There is early evidence from a New York prospective study suggesting that involvement in leisure activities may be protective against dementia.(Verghese ea, 2003) Also, an eastern Finnish prospective cohort study (Häkansson ea, 2009) found that people living in a couple relationship at mid-life had a reduced risk of cognitive impairment later in life compared to those who were single, separated, or widowed.

Occupational therapy in the community improves patient functioning and reduces carer burden.(Graff ea, 2006)

Aetiology²⁷³⁹: The World's human population is getting older, which may explain why so many dementing disorders only received intense medical attention during the last 100 years or so.²⁷⁴⁰ Older intellectually

²⁷³² Annual cost per person in a care home is £31,263. Total UK cost for late-onset dementia is £17.03 bn – includes informal care, lost income, loss of tax revenue, accommodation, and social and health services, but doesn't include various allowances.

²⁷³³ 0.4% at age 55-59 years up to 43.2% among those at least 95 years old.

²⁷³⁴ Burns and Iliffe (2009a) suggest that Alzheimer's disease (AD) causes 50% of cases of dementia, vascular cases (VDm) make up 25%, mixed AD/VDm accounts for 25%, Lewy body dementia (LBD) is present in 15%, and all others make up 5%. The astute observer will quickly see that this adds up to 120%! Sachdev (2008, p. 335) offers the following 'commonly accepted relative frequencies': AD, 50%; vascular, 15%; mixed AD/vascular, 20%; LBD, 17%; frontal, < 15%; 'subcortical' (progressive supranuclear palsy, Huntington's disease, Parkinson's disease), 4%; alcohol, 6%; normal pressure hydrocephalus, 5%; trauma/anoxia/infection, 3%; and prion disease, 2%. In truth, there seems to be no consensus.

²⁷³⁵ See *Alzheimer's and Dementia* 2008 doi:10.1016/j.jalz.2008.01.001 for University of Michigan suggestion that cognitive decline is decreasing in over-70s in the US in association with better education and personal wealth: cognitive impairment fell from 12.2% in the 1993 cohort to 8.7% in the 2002 cohort.

²⁷³⁶ N = 442. Average time in order = 54 years. 104 cases of dementia identified.

²⁷³⁷ 11-labeled Pittsburgh Compound B adheres to beta-amyloid plaques in brain.

²⁷³⁸ Docosahexaenoic and arachidonic acids are important essential fatty acids, required in laege quantities by the developing brain. The human brain is poor at synthesising these and they are chiefly acquired in the diet: fish and seafood, and breast milk (depending on mother's diet) are good sources.(see Hibbeln ea, 2007)

²⁷³⁹ See Gupta ea (2009) for a discussion of some rare dementing disorders.

²⁷⁴⁰ Between 1900 and 1998 the percentage of the British population aged over 65 years increased from 5 to 17. The number of people with dementia is said to rise in the UK by 61% from 2008 to 2026. The percentage of the Irish population aged at least 65 years was predicted to reach 16.4 in 2026. GPs may feel that early diagnosis serves little purpose (or that they do not have the necessary training) but this needs to be challenged.(Anonymous, 2008a)

disabled people, even when Down's syndrome is excluded, are at increased risk of developing dementia, often developing dementia at a younger age than is usual in the general population. (Strydom ea, 2009) Commonly the mechanism is widespread neuronal 'fall out' (i.e. loss) from the cortex. Rarely is the cause centrencephalic. The percentage of the demented population that consists of potentially reversible causes has varied from 3.8-37% in the work carried out by general medical services.²⁷⁴¹ This figure tends to be lower among psychiatric referrals, 4.7% in one study. The reasons for testing such cases are to find treatable cases and to discover conditions that aggravate an underlying dementia. Any physical illness either within or outside the cranial cavity is a potential cause of dementia. Volatile inhalants can possibly cause dementia in young people.

Abnormal folding of proteins may be crucial in the genesis of dementia of various aetiologies, e.g. a toxic increase in function mutation leading to the development of toxic aggregates (beta-amyloid, huntingtin, alpha-synuclein, superoxide dismutase, etc). (Morimoto, 2006)

Taxonomy of neurodegeneration (Lovestone, 2002, p. 289)

Synucleinopathies – dementia with Lewy bodies, Parkinson's disease, multiple system atrophy

*Tauopathies*²⁷⁴² – progressive supranuclear palsy, frontal lobe dementias

Amyloidopathies – CJD, British familial dementia

Alzheimer's disease can be classified under any of the above three headings

Clinical features²⁷⁴³: The clinical features of dementia in general include poor comprehension, social disability, normal level of consciousness, focal deficits (such as aphasia or hemiplegia), and single or double incontinence. Use of aids by the patient to remember (notepads etc) is common. Admission to a long-stay facility ward is more frequently precipitated by social problems than by medical or psychiatric considerations. However, many demented leave the gas flowing or the hall door open, accuse innocent people of stealing their goods²⁷⁴⁴, fall and injure themselves, cause fires whilst smoking in bed, get lost easily (topographical memory loss), expose themselves, or wander aimlessly. Confusion mounts because of say mild infection, subdural haemorrhage, or injudicious use of hypnotics. Interest and activity are narrowed and decreased, and self-neglect becomes marked. Cerebration is slowed down and literalism and concreteness characterise thinking. The latter is usually investigated by asking for the meaning behind proverbs, such as 'a stitch in time saves nine'. Judgement is impaired. Social taboos are innocently flouted, as when the once-prim lady enters the street in incomplete attire. Recent memory departs before that for remote events. Apathy, mood swings, fatuousness, rambling and repetitive conversation, irrelevant statements, aphasia, and an exaggeration and coarsening of personality traits add to the degradation caused by this syndrome.

*Behavioural and psychological symptoms of dementia (BPSD)*²⁷⁴⁵ have recently become a major focus of attention. Although extremely common (Savva ea, 2009), the components of this category vary enormously between people with the same form of dementia, between different dementias, and in individual cases over time. It is important to seek out underlying causes for 'challenging behaviour', e.g. depression²⁷⁴⁶. Various alternatives to antipsychotic drugs have been suggested for BPSD, e.g. trazodone, combined

²⁷⁴¹ In one study (Renvoize, ea, 1985) the percentages of physical and psychiatric disorders on admission in 150 demented patients were folate deficiency (44.8), B12 deficiency (14.6), anaemia (14.2), chest infection (13.3), urinary tract infection (13.3), cardiac failure (11.3), alcohol and drug abuse (4.0), and depression (4.0). Less common diagnoses were diabetes mellitus, drug intoxication, neoplasms, renal failure, other infections, heart block and, in 0.7%, hypothyroidism.

²⁷⁴² Abnormal phosphorylation of tau may inhibit binding of tau to microtubules resulting in tau aggregation and formation of neurofibrillary tangles.

²⁷⁴³ Since the 1960s the cognitive approach to describing dementia has become more popular than the older one of psychotic syndromes. One of the latter was presbyophrenia (manic-expansive dementia) in which the patient was very excited. In dementia, there may be shrinkage of the milieu (less interests), organic orderliness (rigid, stereotyped routines) and catastrophic reactions (sudden explosion of anger if pushed too far to complete a task – 'sham rage' consists of excessive rage reactions to trivial stimuli in patients with posterior hypothalamic lesions).

²⁷⁴⁴ Is this a true delusion? Partly the person cannot remember where the 'stolen' property was placed and concludes that another person took it. Whilst the belief is held with conviction despite evidence of the belief being untrue, this is mainly because the sufferer does not understand the evidence rather than simply that he/she simply rejects evidence.

²⁷⁴⁵ Apathy, sleep difficulties, anxiety/agitation/irritability, feeling persecuted, depression, misidentification, confabulation, hallucinosis, and wandering are listed by Savva ea.(2009)

²⁷⁴⁶ Depression seems to be more common in vascular and Lewy body dementias than in Alzheimer's disease.

benzodiazepine-chlormethiazole (Byrne *et al.*, 2008, p. 363), aromatherapy²⁷⁴⁷, bright light, and diversion techniques. In the opinion of Treolar *et al.* (2010), if a demented patient is obviously distressed and no treatable cause can be found the clinician should discuss the risks and benefits of antipsychotic drug use with carers and relatives and when there is agreement a trial of such medication is ethical. This author agrees.

Causes of rapidly progressive dementia

Subdural haematoma

Vasculitis

CNS lymphoma

Brain neoplasia (primary or secondary)

CJD²⁷⁴⁸

Non-convulsive epileptic status

Various causes of meningitis and encephalitis, e.g. tuberculosis, mycoses, herpetic infection, carcinomatosis and paraneoplasia

Alzheimer's disease is rarely rapidly progressive

Some cases of multi-infarct dementia can progress rapidly

Xie *et al.* (2008) followed up dementia patients in England and Wales. These were drawn from primary care population registers. Estimated median survival time from dementia onset was 4.1 years for men and 4.6 years for women. The older one was at onset the fewer years one survived. Disability also shortened survival time.

Subcortical dementia²⁷⁴⁹ (**SCD**): This represents an attempt to split the dementias into cortical and subcortical types (and indeed, mixed types, e.g. vascular). Subcortical dementia is caused by a disorder of subcortical structures such as the striatum or brainstem nuclei. The differential diagnosis includes Parkinson's disease, idiopathic basal ganglia calcification, spinocerebellar degenerations, progressive supranuclear palsy, Huntington's disease, Wilson's disease, thalamic degeneration or tumour²⁷⁵⁰, infarction of the basal ganglia and thalamus, granulomatous and post-encephalitic involvement of the basal ganglia and thalamus, and parathyroid dysfunction.

Clinical features

Acquired intellectual impairment

Forgetfulness and slowing of mental processes as the primary abnormality

Intellectual deterioration characterised by difficulty in manipulating acquired knowledge

Personality and affective changes that include apathy and depression

Functions of language, calculation and learning remain intact

Proponents of the division insist that these features contrast sharply with the manifestations of cortical dysfunction in AD and its analogues where aphasia, amnesia and agnosia are salient features and intellectual impairment is paramount. Turner *et al.* (2002) point out that there is some evidence that frontal executive dysfunction and memory deficit profile, as well as neuropathological findings, may overlap in SCD and cortical dementia.

Patients with AD do not show improved memory performance when provided with multiple choice options or clues, where those with dementia of depression or subcortical dementia may show improvement.

'White matter dementia' (Filley, 2003)

²⁷⁴⁷ Aromatherapy (e.g. lavender) can be applied to the skin or by inhalation. The oils used contain terpenes (hydrocarbons from plants such as conifers) that are lipid soluble and freely enter the brain.

²⁷⁴⁸ Replication of normal protein that has assumed an abnormal configuration (prion) so that it becomes infectious or, in the case of new variant CJD, transmission of bovine spongiform encephalopathy.

²⁷⁴⁹ The first description of this heterogeneous group of disorders with a common preferential involvement of subcortical grey matter structures was by Kinnier Wilson in 1912.

²⁷⁵⁰ **Tumours of the thalamus** may lead to a severe, rapidly developing dementia, with or without personality change or neurological signs (e.g. abnormal pupillary reflexes).

Proposed term covering cognitive disorders secondary to wide range of disorders

Causes: MS, toluene poisoning, SLE, B12 deficiency, Binswanger disease, trauma, gliomatosis cerebri,²⁷⁵¹ normal pressure hydrocephalus, AIDS dementia complex, etc

Main group features are inability to sustain attention, poor memory retrieval, visuospatial deficits, frontal lobe dysfunction, psychiatric problems, with preservation of language, procedural memory,²⁷⁵² and extrapyramidal function

Alzheimer's disease²⁷⁵³ (AD)

AD affects relatives four times more often than unrelated persons and more women²⁷⁵⁴ than men, although 35% have no family history of AD. It can arise as early as the late forties. The duration is said to be about five years before death following diagnosis.²⁷⁵⁵ There is a steady downhill course although cognitive decline may be accelerated by delirium.(Fong ea, 2009) The core DSM-IV features are memory impairment (impaired learning of new information or recall of previously learned information) and one or more of aphasia, apraxia, agnosia, and disturbed executive function.

Gene-environment interaction²⁷⁵⁶ provides the most likely pathogenic model for AD. AD is found significantly more often in Down's syndrome and Down's syndrome births are more prevalent in families containing cases of presenile AD.(Murphy & Wetter, 2002) The gene encoding beta-amyloid, a prominent component of neuritic (senile) plaques, is near the AD disease locus on chromosome 21.

Early onset AD has been linked to 21 q21 in c. 10% of such families (APP or amyloid precursor protein²⁷⁵⁷; APP gene = β -protein²⁷⁵⁸ or A4-amyloid gene), 14 q24 in most such families (PS1 or presenilin 1), and 1 q31-42 (PS2 or presenilin 2²⁷⁵⁹) – presenilins are secretases involved in beta-amyloid protein production. Early-onset cases show faster cognitive decline than do late-onset cases, and van der Vlies ea (2009) found that a more aggressive course is associated with absence of APOE ϵ 4.

Late onset AD has been linked to 19 q13 (APOE ϵ 4 or apolipoprotein E type ϵ 4 - increases risk but is not essential²⁷⁶⁰) and possibly 12p (White Americans with FAD of late onset; effect of locus occurs mainly if lower loading for ApoE ϵ 4).²⁷⁶¹

²⁷⁵¹ **Gliomatosis cerebri:** In this rare disorder neoplastic cells spread out diffusely through the brain after starting in white matter, including corpus callosum. Cerebral cortex and basal and other nuclei become involved eventually. Other rare malignant causes of dementia are **malignant angioendotheliosis** (variable degree of vascular occlusion by cancer cells) and **lymphomatosis cerebri** (most cases of CNS lymphoma present as single or multiple mass lesions but the diffuse form can present with dementia).

²⁷⁵² **Procedural memory** is memory for non-conscious motor sequences. It is less inclined to be compromised in the brain injured than is memory for information based on language or vision. **Declarative memory** (DM) is more vulnerable in such cases. DM includes *episodic* (recollection of events) and *semantic* (memory for facts) memory.

²⁷⁵³ Alois Alzheimer described his condition in 1906 in a 51-year old female. This common disorder, from which the actress Rita Hayworth died, originally thought to be a rare presenile dementia. The website of Alzheimer's Disease International is at <http://www.alz.co.uk>. The senile form of AD was formerly known 'senile dementia' and is still often referred to as 'senile dementia of the Alzheimer type' (SDAT). See Burns and Iliffe (2009b) for a recent review.

²⁷⁵⁴ Cumulative risk at age 65 years for developing AD at age 95 years is more than twice as high in females compared to males.(Leon ea, 1998)

²⁷⁵⁵ Although this author noticed the first sign of it in his father (getting lost on a familiar route) 13 years before death, although there were hints prior to this (e.g. narrowing of interests).

²⁷⁵⁶ Loneliness is associated with lower cognition at baseline and increased risk of later dementia in later life.(Wilson ea, 2007) Which is the cart, and which is the horse? A high cortisol level plus APOE- ϵ 4 allele status worsens cognitive function in population-based older people and the more of such alleles there are the worse the worse is cognitive function.(Lee ea, 2008)

²⁷⁵⁷ APP is a ubiquitous membrane protein with a large extracellular and domain and a shorter intracellular carboxy terminus. The first mutation found in the APP gene ('London mutation': V717I) was discovered in a kindred whose AD was confirmed at autopsy. A number of other mutations were discovered since but they only account for one in twenty early-onset cases. Duplication of the APP gene in early-onset AD was reported in 2006.

²⁷⁵⁸ Amyloid β -protein (A β) is a central component of neuritic plaques. It is derived from β -APP after beta- and alpha-secretase cleavage.

²⁷⁵⁹ Mutations in presenilin 2 are most frequent in the relatively (genetically) isolated USA-resident Volga Germans.

²⁷⁶⁰ **APOE**, a plasma lipoprotein (gene on chromosome 19), is synthesised by astrocytes and is the most important CNS carrier of cholesterol. A study in the US (Caselli ea, 2009) found that age-related memory decline diverged from that of non-carriers before age 60 years, despite continued normal cognitive status.

The cholesterol ester transfer protein (**CETP** – gene at 16q21) helps regulate cholesterol particle size. Substitution of valine for isoleucine in CETP is associated with lower CETP serum concentration and activity and with increases in HDL. Sanders ea (2010) found preliminary evidence that CETP valine (instead of isoleucine) homozygosity is associated with slower memory decline and incident dementia and AD.

SORL 1 (neuronal sortilin-related receptor) is a neuronal apolipoprotein E receptor and mutation of the gene (on chromosome 11) for this receptor is a marker for late-onset AD (Rogaeva ea, 2007): reduced expression of SORL 1 is found in AD brain and this situation is associated increased amounts of beta-amyloid in laboratory tests.

APP, PS1, and PS2 mutations lead to excess of the pathogenic long-chain amyloid beta protein (A β 42). Also, PS1 protein (gamma secretase) is important in producing A β 42 protein.

Work done in Belfast (Carson ea, 2007) suggests that a haplotype of the alpha-7 nicotinic ACh receptor gene (CHRNA7) may reduce the risk of developing AD. This was independent of APOE status.

The *amyloid cascade hypothesis* states that A β 42²⁷⁶² is a crucial element in the early stages of AD.²⁷⁶³ (Hardy & Selkoe, 2002; Citron, 2004)

In typical clinical practice most cases of AD appear to be sporadic, less than half of cases having a family history²⁷⁶⁴. Bell (2004, p. 68) states that about 10% of cases of AD are familial. Familial AD (FAD) with clear autosomal dominant transmission may make up less than 1% of all cases of AD. Jayadev ea (2008) retrospectively studied adults where both of their parents had suffered from AD and found them to be at increased risk for AD. The risk²⁷⁶⁵ increased with age and was only partly explained by APOE ϵ 4 status. Twin studies²⁷⁶⁶ in late-onset AD suggested a heritability of 0.6-0.7. (Bergem ea, 1997) In the Swedish Twin Registry (Gatz ea, 2006) it was estimated that AD had a heritability of 58%. Seshadri ea, (2002) in an 8-year follow-up Boston study, found that plasma homocysteine levels to be associated with an increased risk for developing AD²⁷⁶⁷. This finding was independent of other risk factors, including apolipoprotein E genotype and B vitamin levels. However, homocysteine levels were performed in non-fasting subjects and not all subjects had their B vitamin levels measured. Prospective studies of vitamin B supplements are required. Folate, which decreases homocysteine levels, might reduce the risk for AD. (Durga ea, 2007; Luchsinger ea, 2007)

Inflammation occurs in AD. Microglia are activated with increased expression of cell surface antigens. They are ineffective in attempts to removing plaques in AD which might be due to partial microglial activation or to the slow process of the disease causing these cells to become 'used to' their presence. Cytokine levels have been described as increased by some authors but not by others. There is the suggestion that apoptosis suppresses the synthesis of pro-inflammatory molecules by microglia. (e.g. Di Simone ea, 2003)

It has been suggested that cognitive impairment may not occur until at least 50 ml of brain tissue has been affected²⁷⁶⁸. Larson (1993) listed risk factors for AD as old age and a family history of AD. To these may be added head injury²⁷⁶⁹ (increased A β deposition in plaques), Down's syndrome, and specific chromosomal mutations (apo E4, for example). Obesity may be a risk factor for dementia, (Gustafson ea, 2003; Whitmer ea, 2005), possibly with a vascular basis.²⁷⁷⁰ However, a common allele of the obesity-related FTO gene may play a role. (Hoa ea, 2010) Kenya ea (2009), in a follow-up study of elderly males and females (N = 3,054) enrolled in a health study, found that obesity was associated with cognitive decline

²⁷⁶¹ All presenilin mutations distort APP processing by promoting secretion of the longer form of A β peptide.

²⁷⁶² A 42-amino acid peptide and proteolytic product of a large transmembrane A β precursor protein.

²⁷⁶³ The A β 42 N-terminus is released by beta-secretase converting enzyme (BACE). BACE and its homologue BACE2 are transmembrane aspartic proteases. The C-terminus of A β 42 is released by an intramembrane gamma-secretase cleavage of the A β precursor protein by a complex consisting of presenilin, nicastrin, APH anterior pharynx defective 1, and presenilin enhancer 2. BACE may prove to be a therapeutic target, using reticulon. Reticulon, a member of a family of receptor-associated proteins, appears to sequester BACE and regulate its activity. Trials are also ongoing of A β 42-brain clearance by immune and non-immune mechanisms. (Selkoe, 2001)

²⁷⁶⁴ However, relatives may die too early to develop AD or cases may not be recognised as such.

²⁷⁶⁵ The risk was 31% and 41.8% in those over 60 and 70 respectively, but 79% of the subjects were still younger than 70 years.

²⁷⁶⁶ Higher pairwise concordance in MZ than in DZ twins.

²⁷⁶⁷ A 5 μ mol increase in homocysteine plasma level increased the risk for AD 40%.

²⁷⁶⁸ However, Snowdon ea (1996) found low density of ideas at age 18 years to be strongly correlated with post-mortem AD pathology among nuns.

²⁷⁶⁹ Mehta ea (1999) could not confirm head injury as a risk factor in a large cohort study, which suggests that the reported association in case-control studies might have been due to recall bias or selective mortality.

²⁷⁷⁰ **Vascular problems in AD:** Purandare ea, (2006) based on a case-control study, suggest that spontaneous cerebral emboli may be important in the pathogenesis of both Alzheimer's and vascular dementias. Helzner ea (2009) found that a higher pre-diagnosis total cholesterol and low-density lipoprotein concentrations and a history of diabetes were associated with faster cognitive decline in patients with incident AD.

in men and not in women. Proposed protective factors (Burns & Murphy, 1996) are education, smoking²⁷⁷¹, moderate drinking²⁷⁷² (controversial), NSAIDs, and oestrogens²⁷⁷³. The P300 is a large, positive delayed wave on the EEG which occurs 300 milliseconds after a stimulus. The latency of the P300 is significantly longer and the amplitude significantly smaller in the AD than in comparison subjects. A pathological delay occurs 20 years earlier in Down's syndrome than in controls. The P3 of the olfactory event-related potential (OERP) shows longer latencies in AD²⁷⁷⁴ than in age/gender-matched controls and may be a better discriminator for AD than the auditory event-related potential. Possession of the ApoE ϵ 4 allele also increases the latencies of the OERP, but by less than that associated with AD. (Murphy & Wetter, 2002) Odour identification, odour threshold, and odour recognition memory are abnormal in Down's syndrome; OERP P3 latencies increase in Down's syndrome with increasing severity of dementia. Also, there are increased P3 delays in visual and auditory event-related potentials in Down's syndrome. In SDAT, both PET and SPET studies show a characteristic reduction in the posterior temporoparietal regions that can be temporarily reversed with physostigmine, a cholinergic agonist. Beacher ea (2009) compared Down's syndrome patients with and without AD using volumetric MRI. Those with AD had significantly smaller hippocampi and caudate nuclei and right amygdala and putamen.

Schupf (2002) reviewed factors promoting dementia in Down's syndrome. Apolipoprotein E ϵ 4 allele, oestrogen deficiency and high levels of $A\beta$ 1-42 peptide are associated with earlier onset of dementia. Atypical karyotypes and apolipoprotein E ϵ 2 allele are associated with lower mortality and lessened risk of dementia.

The notion that AD results from exposure to electromagnetic fields²⁷⁷⁵ has not been adequately researched. Researchers should study exposure directly rather than infer exposure on the basis of occupation (e.g. electrician). This has been done in a controlled experiment (Landgrebe ea, 2008) using transcranial magnetic stimulation (rTMS) to the prefrontal cortex. 40% of the hypersensitive group and 60% of matched controls could feel no sensation when given sham stimulation. The authors found 'significant cognitive and neurobiological alterations pointing to a genuine individual vulnerability of electromagnetic hypersensitive patients'. Interestingly, Cotelli ea (2010) found that rTMS (20 Hz, 25 minute sessions, 5 days/week for 4 weeks) applied to the prefrontal of moderate AD patients (N = 5) improved correct answers on a comprehension test from 66% to over 77% compared to similarly affected subjects (N = 5) given a 'sham' (dummy for 2 weeks, rTMS for next 2 weeks) treatment. Other cognitive abilities and memory were unchanged. These results are preliminary.

Braak²⁷⁷⁶ staging of Alzheimer-type pathology

Stages 1 + 2: entorhinal

Stages 3 + 4: limbic

Stages 5 + 6: neocortical

The neuropathology is complex²⁷⁷⁷. There is loss of cortical neurones²⁷⁷⁸ with wide sulci and shrunken, narrow gyri. Argyrophilic senile (neuritic) plaques with amyloid in their cores (the more plaques the deeper the dementia) are also found. One description of these plaques was that they begin as a cluster of abnormal neurites (dystrophic axonal or dendritic terminals) without amyloid cores and progress into a mature or

²⁷⁷¹ Long-term tobacco use reduces $A\beta$ deposition. (e.g. Court ea, 2005) The effect of smoking has been reported to increase and to decrease risk for AD. One possible reason for a false protective report would be the early death of smokers, i.e. smokers are less likely to figure in AD cohorts. Fratiglioni ea (2008, p. 395) suggest that smoking is a risk factor for dementia. Passive smokers may suffer cognitive impairment. (Llewellyn ea, 2009)

²⁷⁷² Heavy drinking may be a risk factor for dementia in late life, particularly in conjunction with the APOE ϵ 4 allele. (Antilla ea, 2004)

²⁷⁷³ Removal of guinea pig ovaries leads to excess beta-amyloid in brain.

²⁷⁷⁴ Unlike other sensory cortices, there is involvement of the primary olfactory cortex and the peripheral olfactory cortex in AD and these are associated with olfactory deficits in excess of those expected in old age.

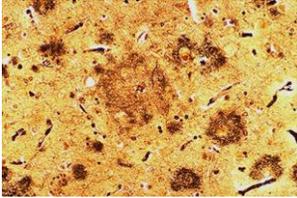
²⁷⁷⁵ The modern citizen is exposed to electromagnetic fields arising from the presence of electric equipment, including mobile phones. Many non-specific symptoms have been blamed on such exposure, e.g. skin and GIT problems, poor concentration, sleep difficulties, and tiredness.

²⁷⁷⁶ After Frankfurt anatomists Heiko and Eva Braak. See Braak and Braak. (1991) According to Nagy ea (1999 –the Braak group) dementia symptoms develop during stages 3 and 4.

²⁷⁷⁷ The large community-based study of Esiri ea (2001) found that most non-demented people's brains have some features of AD or cerebrovascular disease.

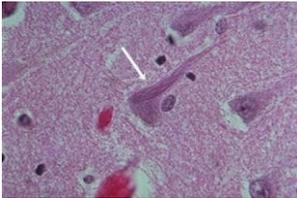
²⁷⁷⁸ Especially in the hippocampus, neocortex, locus ceruleus, and nucleus basalis.

classical plaque, with central amyloid surrounded by numerous neurites and some astrocytic processes and microglia. Diffuse plaques are deposits of beta-amyloid without a surround of degenerating nerve cells whilst neuritic plaques have a core of beta-amyloid surrounded by dystrophic neurites whilst the whole is surrounded by activated microglia and reactive astrocytes.



Amyloid plaque

Studies of neurotransmitters during the 1980s suggested that the primary lesion is cortical and that the pathology may originate with plaque formation in the hippocampus/amygdala, although other studies suggest that the pathology may commence in subcortical structures such as the basal nucleus. Neuritic plaques are largely found outside cells, whereas the tangles are found inside cells – the number of tangles, but not of plaques, correlate (subject to great inter-individual variability²⁷⁷⁹) with clinical degree and duration of dementia (however, soluble beta amyloid more strongly correlated with severity of dementia than do plaque counts). There are neurofibrillary tangles (helically paired twisted filaments: intraneuronal bundles of phosphorylated tau proteins) in the neuronal perikarya (occasionally in neurites) and in pyramidal neurones of the hippocampus, entorhinal cortex and neocortex, nucleus basalis of Meynert, and periaqueductal grey matter²⁷⁸⁰.



Neurofibrillary tangle

Alzheimer tangles contain a fragment of tau²⁷⁸¹, a protein normally associated with the microtubules that are responsible for rapid axonal transport in the healthy brain. Also described is granulovacuolar degeneration of Simchowicz²⁷⁸² and congophilic angiopathy²⁷⁸³.

Chronology of selected AD research (from 1990)

1990. 3 pairs of elderly MZ twins discordant for AD.

National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria predict probable and possible AD with sensitivities of 88% and 78% respectively – criteria checked against histology. (Definite AD requires both clinical and pathological data.)

AD cases show depression less often as the illness advances whereas multi-infarct dementia cases can be depressed at any stage.

Early in AD, an amyloid A4 protein, derived from a large precursor protein coded on chromosome 21, is deposited in parenchymal plaques and in cerebral vessels. Cerebral cortex and sub-cortical nuclei are most affected. Cell damage causes neurotransmitter loss, the most consistent damage being to cholinergic neurones connecting sub-cortical nuclei to cerebral cortex. Postsynaptic muscarinic cholinergic receptors are usually intact. Ascending noradrenergic and serotonergic pathways are also damaged, especially in younger patients.

65% of carers of dementia sufferers experienced significant stress. Most at risk were females and younger carers. Stress in carers was associated with high levels of physical disability but not with degree of cognitive impairment.

In primary dementia, population of locus coeruleus neurones most extensively reduced in depressed patients, and such patients have a much greater reduction in noradrenaline levels than do non-depressed patients.

²⁷⁷⁹ E.g. it is quite possible for a mildly cognitively impaired person to have a very high tangle count at post-mortem and, for early cases, *vice versa*.

²⁷⁸⁰ They are rarely, if ever, seen in Purkinje's cells or in lower motor neurones.

²⁷⁸¹ 60, 64 and 68 kDa

²⁷⁸² Small, clear, intraneuronal cytoplasmic vacuolation, each vacuole containing one argyrophilic granule.

²⁷⁸³ Amyloid infiltration of blood vessel walls and adjacent perivascular neurophil (aka **neuropil**, i.e. axons + dendrites collectively).

Huntington patients more aggressive and apathetic than AD cases, and irritability related more to premonitory poor temper control in Huntington patients than in AD cases. (Study using scales)

1991. Variation in age of onset in cases of early onset FAD is produced by interfamily variations, but within families it tends to be constant.

In early onset AD smoking was associated with a reduced risk of AD and at least a 4-year delay in onset of AD.

The risk of dementia in first-degree relatives is about the same whether the dementia is due to AD or not.

Prognosis in dementia over 4 years not predicted by scores on parietal tests, but high scores for global cognitive impairment predicted early demise.

Using isoelectric focusing, an abnormal band found in acetylcholinesterase in CSF of AD patients.

Putative linkage reported of late-onset AD to chromosome 19.

1992. β -Amyloid is neurotoxic but animal studies equivocal.

Patients with FAD have a faster course of illness and stronger family history of psychiatric disorders v patients with non-familial AD – these may reflect genetic or environmental differences between the 2 groups.

FAD seems to transmit as an autosomal dominant trait. Mutations of the gene coding for APP have been identified. β -Amyloid protein (normally produced in soluble form, but present in insoluble form in AD) is cleaved from APP.

Discovery of second gene FAD on chromosome 14: AD likely to be aetiologically heterogeneous.

1993. Retrospective Scottish study finds female sex positively associated with development of AD before age 65 years.

Replication reported of early onset FAD gene on chromosome 14q.

It is probably not β -amyloid production per se that is neurotoxic, but rather the aggregation of insoluble β -amyloid.

SPECT using Tc^{99m}-HMPAO: AD showed reduced uptake in all regions, especially in temporal (important for memory) and posterior parietal areas, duration of illness correlating with reduced uptake in most brain regions.

1994. AD is fourth major cause of death in developed world.

Morphological brain damage may promote psychotic phenomena, e.g. depression, hallucinations, paranoid delusions, and delusional misidentification.

Mothers of Down's syndrome probands are at increased risk for non-stroke dementia.

AD disease associated with neuronal loss in CA1 region of hippocampus, an area relatively preserved in normal ageing.

Familial contribution to risk for 'primary progressive dementia' decreases with increasing age and is very low or non-existent by latter half of ninth decade.

Earlier onset of AD may be related to the presence of more language and praxis impairment, and greater depression during the illness.

1995. Against the idea that AD equates with old age is its absence in a 118 year old French woman.

Transgenic mice produced that express high concentrations of human amyloid precursor protein and progressively develop many, but not all, of the pathological hallmarks of AD.

Gene responsible for many cases of presenile FAD on 14q cloned and mutations characterised.

A number of mutations in S182 gene on chromosome 14 and another in a homologous STM-2, on chromosome 2, may cause early-onset FAD.

Meta-analysis suggests that the very old may be less prone to develop AD than are the old i.e. the rate of increase falls off.

Patients with AD plus psychosis had relative (to right side) hypoperfusion of left frontal lobe (not so with AD only).

Scottish study suggested that increased paternal age increased the risk for presenile AD in male offspring only.

Early CT volumetric changes may help to distinguish early, mild AD from normal ageing.

β -Amyloid in peripheral blood vessels damages endothelial cells by producing superoxide radicals. This process can be blocked by superoxide dismutase (which mops up superoxide radicals). It remains to be proved that this occurs centrally.

No link found between cognitive dysfunction in the elderly and antihypertensive therapy.

15-year follow-up of 70 year olds found that hypertension was associated with increased risk for AD and/or multi-infarct dementia, but blood pressure tends to fall before onset of dementia.

APOE ϵ 4 allele may have a dose effect that increases risk and brings the disorder forward in time.

1997. 83% of family members accompanying patients with AD to memory clinic did not want patient told diagnosis – but 71% would want to be told if they had AD!

Pairwise and probandwise concordance for AD among MZ and DZ twins were 78% plus 39% and 83% plus 46% respectively. No significant difference in rate of apolipoprotein E ϵ 4 allele between twin pairs concordant and discordant for AD. Estimated heritability was about 0.6.

APOE ϵ 4 allele is a risk factor for AD but no support found for a strong association between APOE ϵ 4 dosage and the rate of cognitive decline. Also, the APOE ϵ 4 allele did not predict age of onset.

Controlled study using PET plus radiolabelled acetylcholine analogue found decreased acetylcholinesterase activity in AD brain, especially in temporal (31% decrease) and parietal (38% decrease) areas.

1998. Age-specific prevalence rate of AD in Down's syndrome reached 40% in the 50-59 year age group.

Late onset AD is a common familial disease involving several genes and environmental factors.

1999. Depressive symptoms may be early manifestations rather than predictors of AD.

Corticotrophin releasing factor immunoreactivity reduced in mild and severe dementia but somatostatin-like immunoreactivity reduced in severe cases only.

2000. Significant excess of APOE ϵ 4 in demented v non-demented Down's patients.

Both magnitude and extent of brain activation (MRI during memory testing) in regions affected by AD (including left hippocampal, parietal and prefrontal) were greater among cases with ϵ 4 allele than in those with ϵ 3 allele. During periods of recall, carriers of ϵ 4 allele had greater average increase in hippocampal signal intensity and greater mean number of activated brain regions than did ϵ 3 allele carriers.

Deficits in olfactory identification detected by University of Pennsylvania Smell Identification Test may have clinical utility as an early marker for AD.

Dutch study of centenarians assessed 15 of 17 people over 100 (in one area) and found all were demented, 12 having greater than mild dementia.

- 2001.** Microglial activation occurs early in course of AD. PET revealed parietal/temporal/prefrontal deficits in glucose metabolism in cognitively intact APOE ϵ 4-positive individuals.
- 2002.** Homocysteine may have an aetiological role. Trials of a vaccine (AN1792) being developed by ELAN (Ireland)/Wyeth suspended after 12 volunteers became ill (aseptic meningoencephalitis); autopsy on one case showed less brain amyloid than expected. When predicting AD in patients with mild cognitive impairment, CSF-CBF index (tau levels \div regional cerebral blood flow in posterior cingulate cortex on SPECT; using cut-off value of 296) gave sensitivity of 88.5% and specificity of 90%.
- 2003.** Workers assessed and followed up 1435 Swedish non-demented people aged 75-95 years for three years and found that only 18% of future dementia cases could be identified. Feeding tubes do not increase survival rates in dementia and can have significant adverse effects.
- 2004.** Study of diagnostic accuracy of CSF concentrations of tau proteins phosphorylated at 3 pathologically important epitopes²⁷⁸⁴ (p-tau) – AD, other dementias, and normals – in terms of sensitivity and specificity, these proteins ‘come closest to fulfilling the criteria of a biological marker of AD’. Cache County (Utah) Study: estimated 100-year lifetime incidence of AD at 72% (28% would never develop AD). 1 or 2 APOE ϵ 4 alleles accelerated onset of AD but did not determine if one got AD. Both high and no alcohol intake in middle life led to increase in mild cognitive impairment, and, less certainly, to dementia – this has been interpreted as a U-shaped relationship but it could also be spurious.
- 2005.** Vitamin E does not prevent progression from mild cognitive impairment to AD. Whilst donepezil lowers the rate of such progression in the first 12 months of treatment, the rate of progression catches up later. AD pathology is more likely to be clinically expressed as dementia in females than in men. If tau production is turned off in transgenic mice that over-express mutant tau the mice demonstrate improved cognition despite continued neurofibrillary tangle accumulation. Apparent decline in incidence of AD reported in some studies in oldest-old may be an artefact of poor response rates, survival effects, and the populations sampled. Uncontrolled hypertension in middle age increases risk for dementia in old age but hypotension in the elderly is related to the development of dementia.
- 2006.** In later-myelinating regions, severity and rate of myelin breakdown in healthy older people are associated with ApoE status. A lifetime history of depression in AD cases in nursing homes was associated with increased AD-associated neuropathological changes in hippocampus and more rapid cognitive decline. Depression early in AD increases expression of AD-related pathology in hippocampus. Donepezil improves cognition and preserves function in severe AD in nursing homes. Donepezil was of no benefit in chronic schizophrenia regarding cognition or negative symptoms. Mild cognitive impairment plus other cognitive domain deficits (espc. in verbal memory and psychomotor speed/executive function) constitute a higher risk for AD than pure amnesic problems. Heritability of AD in Sweden estimated at 58%.
- 2007.** Whole brain atrophy rates may be greater in cognitively normal ϵ 4 homozygous late middle-aged people than in comparable individuals with no or one copy of apolipoprotein E (APOE) ϵ 4 allele. Inconclusive results with trapirosate, a vaccine that binds to beta-amyloid protein.
- 2008.** Mild cognitive impairment as a predictor of AD is only good for subjects 70-85 years of age, not for younger people. Depressed homebound elderly had lower plasma A β 42 levels and a higher A β 40:A β 42 ratio than controls. 12.7%, 78.8%, and 4.2% of patients attending a Cork memory clinic had mild cognitive impairment, dementia, and depression without dementia respectively. Although immunisation with A β 42 led to clearance of amyloid plaque in AD this did not stop progression of neurodegeneration. 115 year-old Belgian woman had good cognitive function during life and negligible neurodegenerative brain changes at post-mortem. Prevalence of DSM-IV dementia in people aged at least 65 years at 11 sites varied from 0.3% in rural India to 6.3% in Cuba but the criteria may underestimate true prevalence, particularly in the most under-developed regions where there may be problems in defining and ascertaining decline in cognitive function and its consequences. In transgenic AD model mice valproic acid decreased A β production by inhibiting glycogen synthase kinase-3 β (GSK-3)-mediated gamma-secretase cleavage of APP; valproic acid significantly reduced neuritic plaque formation and improved memory deficits; early use of valproic acid is important to alleviate memory deficits.
- 2009.** Association between pathological features of AD and dementia is stronger in younger old people than in older old persons. Older people with extensive age-related white matter changes on MRI are at high risk of functional decline over the following 3 years. The stronger was muscle strength at the start of this study of community-dwelling older people the lower was the risk of developing AD during follow up; the mechanism is unknown (possible mitochondrial damage leading to poor muscle strength and cognitive function, or CNS damage from stroke that reveals subclinical AD, etc).
- 2010.** Carers of community-dwelling people with dementia attending a Dublin service had high levels of met and unmet needs.

Damage to, or loss of cholinergic fibres leads to depletion of enzymes involved in ACh metabolism. Most of the cholinergic loss in AD is presynaptic²⁷⁸⁵. The apparent preservation of receptors is part of the rationale for replacement therapy. Noradrenergic, dopaminergic and serotonergic systems are also impaired. These neurotransmitters are largely made in subcortical structures, such as the nucleus of Meynert and locus ceruleus. Older cases have a mainly cholinergic deficit whereas younger cases have not

²⁷⁸⁴ Epitope = antigenic determinant.

²⁷⁸⁵ Up to 50% of total cortical synapses are lost in AD – synaptophysin immunoreactivity in frontal and parietal cortices and hippocampus correlates with severity of dementia.

only a more widespread and severe cholinergic loss but they also have greater impairment of other neurotransmitter systems. Amongst the enzymes depleted is choline acetyltransferase. Choline replacement has been disappointing. GABA and the catecholamines may also be affected. The balance between transmitters may be more important than the absolute level of any single substance. The brain of the normal resting adult has a respiratory rate of about 3.3 ml. O₂/100g/min. In dementia this falls to about 2.7 ml, about the same as in myxoedema. The reduction is pathological and is not explicable on age grounds alone. Leonard (2003, p. 352) emphasises the fact that not all neuropathologically verified cases of AD have reduced levels of choline acetyltransferase and others have normal numbers of cholinergic cells in the nucleus basalis of Meynert. He also points out that there is gross loss of basal forebrain cholinergic neurones in olivopontocerebellar atrophy with no clinical dementia. (Cf. multiple system atrophy) It is possible that AD may result from abnormal membrane phospholipid metabolism regulation, leading to rigid membranes. Large decreases in brain N-acetylaspartate in cerebral gray and white matter have been found in AD using proton MRS. (Huang *et al.*, 2001) However, the specificity of such findings to one type of dementia is not high.

Studies conducted during the 1980s found that clinico-pathological agreement on diagnosis approached 90%, an increase from 70% of some years previously. However, there is probably a wide disparity in what is meant, clinically, by AD. Some workers proposed a continuum model between senile dementia of the Alzheimer type (SDAT) and normal ageing. However, using PET scanning to measure cerebral metabolism of glucose, and neuropsychological tests, Grady *et al.* (1987) found no support for the existence of different subgroups of AD based on age at onset, or for a faster rate of cognitive decline in younger patients. Aluminium injected into the brains of animals can produce neurofibrillary tangles, but there are ultrastructural differences between aluminium-induced and Alzheimer tangles. It is potentially possible that a genetic defect might facilitate the entry of aluminium into the brain. There is often much more aluminium in food or in medicaments than in water! There is a higher level of aluminium in the water on Guam (see below) but these people get amyotrophic lateral sclerosis, and the water there is also low in calcium and magnesium. Dialysis dementia (high brain aluminium levels, no plaques or tangles) occurs unless the aluminium level has been reduced by purification procedures. Aluminium is used as a coagulant to remove particulate matter containing toxic pollutants in water.

The entorhinal cortex²⁷⁸⁶ is linked with the hippocampal formation, providing the latter with its major cortical input. The cells of origin of the perforated pathway are destroyed in AD and a marked decrease in glutamate (a putative neurotransmitter in its terminal zone) occurs. Identification of odours is impaired early in AD, but acuity of odour detection is impaired only later in the evolution of the disease.

Down's syndrome²⁷⁸⁷ is more likely to occur in families with AD than in families without such a history. In patients with trisomy 21, the 50% increase in all of chromosome 21's genes results in both an increase in the quantity of β -amyloid protein and an acceleration of the deposition of β -amyloid protein in the brain. The presence of excess β -amyloid protein ($A\beta$) within and without the neurone may convert a physiological function into a pathological one by inhibiting axonal protein transport using the same transport machinery as amyloid precursor protein (APP), thereby leading to synaptic dysfunction and death.

Oxidative damage may be important in both vascular dementia and AD. There are many antioxidants in the diet, including vitamins C and E. Those antioxidants may act synergistically as free radical scavengers and it is suggested that vitamin E may protect muscarinic receptors. Levels of the free radical defensive enzyme superoxide dismutase are reduced by 25-30% in the frontal cortex and hippocampus. (Lethem & Orrell, 1997) Trisomy 21, as stated above, is associated with an increased risk for early onset AD and is associated with increased superoxide dismutase activity (because the gene is on chromosome 21 of which the patients has 3 copies). Superoxide dismutase converts the superoxide free radical to H₂O₂ that is then converted to H₂O by other enzymes. In the presence of certain metal ions like iron the H₂O₂ can be converted to the extremely toxic hydroxyl free radical. The excess of superoxide dismutase in Down's syndrome may cause excess production of the hydroxy radical. One piece of good advice is to eat a healthy diet, including fruit and vegetables. (Lethem & Orrell, 1997) A meta-analytic study (Sofi *et al.*, 2008) suggests that adherence to a Mediterranean diet is significantly associated with reduced mortality overall and from cardiovascular and malignant causes, Parkinson's disease, and AD. However, there are many Mediterranean diets and the

²⁷⁸⁶ Islands of cells in layer II of the entorhinal cortex degenerate very early in AD, thus disconnecting neocortex and hippocampus.

²⁷⁸⁷ Even though dementia occurs earlier in Down's syndrome than in the general population it is still rare before age 50 years, despite neuropathological changes being present for about the preceding decade.

study is limited to some degree by adjustment for potential confounders in the studies employed in the meta-analysis.

Alzheimer patients with depression are more cognitively impaired and more disabled than are their non-depressed fellows.

Dementia-Parkinsonism complex of Guam

Guam, New Guinea, and Honshu

Features of motor neurone disease, Parkinson's disease, or AD, or combinations of these

Affected areas share low concentrations of calcium and magnesium in soil and drinking water as well as high concentrations of aluminium and iron, but working in an aluminium factory is not associated with an excess risk for AD

May be some interaction between an environmental insult and aging process because migrants from these areas have developed the condition years later

Plant poison has been suggested - seeds of the cycad containing an analogue of alanine

Retrogenesis

As AD develops, developmental acquisitions are progressively lost in reverse order to their acquirement during development

Person eventually unable talk, walk, etc, and expresses reflexes, like palmar grasp, that were suppressed in earlier life

It is said that AD may have a long history of neuropathological change that precedes clinical symptoms, (Goldman et al, 2001) including hippocampal atrophy on MRI. (De Leon et al, 1997) However, close prospective observation (of, say, close relatives) suggests that there may be hints of incipient dementia during this 'prodrome', e.g. giving up pastimes such as walking or doing crosswords, or irritability when asked to do chores or become involved with grandchildren's' play. Eventually the postman may bring the patient home in a distressed state after the latter becomes lost on a familiar route. High intelligence and the supports provided by others may mask early changes. Loss of support, as through death of a partner, can lead to a crisis. Early onset AD (say, < 60 years) is more likely to manifest changes in comportment (e.g. disinhibition²⁷⁸⁸), abnormal gait, and extrapyramidal disturbances.

Clinical features of Alzheimer's disease divided into four arbitrary stages

Stage I: Memory and concentration are poor. Fatigue and anxiety increase. The person is restless and experiences fleeting depression²⁷⁸⁹. Premorbid personality characteristics are exaggerated. Antisocial acts or statements occur that are out of character. There may be nominal dysphasia at times, changed handwriting, and perseveration. Medication may compound disability, e.g. confusion from anticholinergic drugs.

Stage II: Work performance deteriorates and the patient may live in squalid surroundings. Dysarthria, reduced vocabulary, poor grammatical construction, logoclonia (reiterating parts of words), echolalia, misspelling and duplication of parts of words, reduced reading ability, reduced ability to comprehend the speech of others, urinary incontinence, epilepsy (5-10%), dyspraxia and agnosia may be noted. The patient may become easily lost. Recent and remote memory is poor. Misidentification occurs (mirror sign, or talking to photographs), as do depression, delusions and hallucinations, especially visual. There are behaviour problems, emotional lability, catastrophic reactions, motor restlessness, phases of inertia, muscular rigidity, and gait apraxia.

Stage III: Gross impairment of all intellectual functions, severe neurological disability (+/- hemiparesis, rigidity, and wide-based unsteady gait), double incontinence, fatuousness, euphoria, jargon dysphasia, emaciation, limb contractures, and inability to recognise anyone including the self.

²⁷⁸⁸ Sexual disinhibition might respond to SSRIs (Stewart & Shin, 1997) or medroxyprogesterone. (Rabins, 1998)

²⁷⁸⁹ There is no direct correlation between stage of AD and depression. (Thomas, 2008, p. 430) Depression is usually of brief duration in demented people and may respond to simple measures such day centre attendance and spending more time with the patient; only severe, prolonged depression requires medication. Depression is a common prodrome of AD and may be a risk factor for AD, perhaps acting via cortisol/HPA axis activation or via vascular pathology.

Stage IV: Death.

Weight loss can be severe in AD, even greater than with cancer.(Thomas, 2008, p. 431)
 Effective treatment focuses on the patient-caregiver unit, not on the patient alone. It is essential that the family and the patient know enough to initiate proceedings to cover financial, health-care and other matters before competence is lost.

Management of AD

Step 1 – non-pharmacological, e.g. behavioural

Step 2 – if 1 fails and behavioural problems persist – cholinesterase inhibitors

Step 3 – if 2 fails and behavioural problems persist - low dose atypical antipsychotics

Physical exercise is inversely associated with the risk of dementia.(Hamer & Chida, 2009) Is this a true prophylactic action or are people with subtle cognitive decline less likely to exercise and so compromise their cardiovascular status?

Treatments have been aimed at replacing neurotransmitters, stimulating intact receptors, and alleviating disturbed behaviour symptomatically.²⁷⁹⁰ Anticonvulsant treatment for aggressive behaviour has been disappointing.(Thomas, 2008, p. 430) It has been tentatively (Martyn, 2003) claimed that NSAIDs like ibuprofen may delay the onset of AD, an effect not found for aspirin²⁷⁹¹ (although Etminanan ea, 2003 found a reduced risk for AD of 13% with aspirin compared to 30% with NSAIDs), acetaminophen,(Stewart ea, 1997) or hydroxychloroquine²⁷⁹². Longer use of NSAIDs appear more protective against AD than shorter use.(Etminanan ea, 2003) Although small clinical trials have suggested a role for oestrogen treatment, a larger trial found no benefit after one year.(Mulnard ea, 2000) Health-seeking behaviour and socioeconomic status of women receiving oestrogens must be controlled for in such research. However, there is some evidence that women who lack the APOE ε4 allele may benefit from oestrogen treatment whereas ε4 negative women may not benefit; the same study suggests that oestrogen may exert its beneficial effects by reducing carotid atherosclerosis.(Yaffe ea, 2000) Nevertheless, there is also evidence suggesting that oestrogen/HRT may be a risk factor for AD rather than protecting against it.(Shumaker ea, 2004; Simard & Sampson, 2008, p. 234) Also, oestrogens have their own adverse effects.

The *anticholinesterases* showed some consistent promise.(see box) They are indicated for ‘mild to moderate’ dementia²⁷⁹³. Most cases experience little in the way of side-effects (mainly GIT and responsive to antiemetics) and such events tend to occur early as doses are titrated. If the patient deteriorates cognitively the anticholinesterase may be slowly withdrawn to see what benefit was being derived from its prescription; if the latter is worthwhile the medication may be continued. Byrne ea (2008, p. 362) suggest that prescription of anticholinesterase drugs should be maintained as long as MMSE scores remain above 12 points and where overall, functional and behavioural status suggests a useful drug effect. Interestingly, these drugs may maintain their effects for some weeks after discontinuation²⁷⁹⁴. The ethical/moral question has been raised as to whether they inappropriately prolong life.²⁷⁹⁵ Apathy may respond to

²⁷⁹⁰ The list of proposed drug treatments includes vasodilators (e.g. isoxsuprine, cyclandelate, dihydroergotoxine, and mixtures of ergot alkaloids like hydergine), precursors of Ach (e.g. choline and lecithin – lecithin is phosphatidyl choline), stimulators of Ach release (e.g. piracetam), inhibitors of Ach hydrolysis (e.g. physostigmine, THA), neuropeptides (e.g. vasopressin and its papaverine analogues – given intranasally), and so-called brain metabolism enhancers (e.g. pyritinol, pentifylline). The selective muscarinic agonist xanomeline may reduce shouting and psychotic phenomena.(Bodick ea, 1997) ‘Disruptive vocalization’ is sometimes due to depression.(Dwyer & Byrne, 2000)

²⁷⁹¹ Aspirin is a COX-1 inhibitor that inhibits platelet aggregation.

²⁷⁹² Hydroxychloroquine may cause anxiety, nightmares, a confusional state, aggression, depression, and mania.

²⁷⁹³ MMSE score 10-24 and duration < 6 months.

²⁷⁹⁴ This raises the question why this is so? Is it persistence of drug in CNS or is it due to muscarinic receptor stimulation causing non-amyloidogenic processing of amyloid precursor protein. Anticholinesterases may slow hippocampal atrophy.

²⁷⁹⁵ Their value in routine clinical practice and foretelling which patients benefit have also been challenged.(Anonymous, 1998; Anonymous, 2000a) A tendency to avoid telling patients that they are suffering from dementia may work against such drugs receiving a trial in such cases.(Wild & Petit, 2002) Knapp (2003) suggests that cholinesterase inhibitors save money spent on institutional care but shifts the economic burden onto family carers (who will have to care for the patient for longer). In 2006 NICE in the UK restricted use of anticholinesterases for AD who have moderate disease (not early or late), a decision challenged by the pharmaceutical industry and the UK Alzheimer’s Society (donepezil is advertised as suitable for all degrees of AD in the US). According to Dyer (2007), prescribers, whilst keeping controversial 2006 NICE guidelines in mind, are not prohibited from

anticholinesterases (Thomas, 2008, p. 430) as may agitation, anxiety, delusions, and hallucinations. (Trinh et al, 2003) Cholinesterase inhibitors have been used²⁷⁹⁶ to treat AD, vascular dementia, delirium, traumatic brain injury, frontotemporal dementia, Korsakoff's syndrome, Huntington's disease, and mild cognitive impairment. (Overshott & Burns, 2005)

Anticholinesterases for 'mild to moderate' Alzheimer's disease

Caution is required with succinylcholine type muscle relaxants (e.g. during ECT) as the relaxant effect (i.e. paralysis) may be prolonged as a result of plasma pseudocholinesterase inhibition: stop acetylcholinesterase inhibitors before procedures requiring use of succinylcholine. Cholinesterase inhibitors increase gastric acid secretion with the risk of bleeding (esp. if there is peptic ulcer or the patient is taking anti-inflammatory medication). They may exacerbate weight loss, COPD²⁷⁹⁷ or asthma, obstruct urinary outflow, increase seizure risk, and cause heart block and sinus bradycardia²⁷⁹⁸ (esp. in cases of supraventricular conduction delay) with the possibility of fainting or falls. There is a theoretical possibility of toxicity from cocaine or cocaine-like local anaesthetics. Butylcholinesterase degrades aspirin, mivacurium and cocaine-like local anaesthetics. Over time, acetylcholinesterase levels fall relative to butylcholinesterase in AD.

(a) *Terahydroaminoacridine*: There has been some evidence for improved cognitive function using the centrally active anticholinesterase THA (terahydroaminoacridine or Cognex, an acridine) but this has fallen from favour because of its hepatic toxicity²⁷⁹⁹ and because not all studies have found it to be effective. THA can cause troublesome cholinergic side effects (e.g. GIT upset and hypotension).

(b) *Donepezil hydrochloride* (Aricept, Aripez, Donesyn, Donecept, Dozept), a piperidine derivative has been said to delay the progress of AD, although a study of community-based 'mild to moderate' cases of AD failed to support this claim. (AD2000 Collaborative Group, 2004; Schneider, 2004) There is some evidence that the rate of progression from mild cognitive impairment to AD may be slowed during the first year by donepezil, but this effect wears off. (Petersen et al, 2005) It is tolerated better and is much less toxic than THA. Donepezil is excreted in the urine and metabolised to multiple metabolites by the cytochrome P450 system. It has a plasma half-life of c 70 hours. It can cause mild and transient nausea, diarrhoea, vomiting, fatigue, insomnia, headache, coryza-like symptoms, dizziness/syncope, bradycardia, heart block, muscle cramps (minor increase in muscle CK), abdominal disturbance, anorexia, hallucinations, agitation²⁸⁰⁰ and aggression. (Anonymous, 1998) The last three neuropsychiatric symptoms tend to resolve if the drug is stopped or the dose is reduced. (Anonymous, 2003a) Other associated problems include enhancement of succinylcholine-like muscle relaxants, vagotonic effects (e.g. bradycardia – may be problematic in sick sinus syndrome or other supraventricular cardiac conduction disorders like sinoatrial or A-V block), urinary retention, and (like AD) seizures. Caution is required in asthmatics or obstructive lung cases. Breakdown of donepezil is inhibited by ketoconazole and quinidine and probably by itraconazole, erythromycin and fluoxetine. There may also be reduced plasma levels of donepezil in the presence of enzyme inducers like rifampicin, phenytoin, carbamazepine and alcohol.

(c) *Rivastigmine* (Exelon²⁸⁰¹), a carbamate, is another acetylcholinesterase inhibitor. Upward dose titration should be slower if there is renal or hepatic dysfunction and the drug should be avoided in the case of

prescribing for 'mild' cases. However, Bayer (2007) points out that the 3 acetylcholinesterase inhibitors in question (donepezil, galantamine, and rivastigmine) were recommended by NICE (following a High Court case) for cases 'of moderate severity only' (MMSE scores 10-20); MMSE and other relevant review should be conducted every 6 months; and the drug should be continued while MMSE score is 'above 10 points'. Naturally, interpretation of the MMSE must take heed of factors such as IQ and linguistics. In 2008 (Dyer, 2008) the appeal court held that NICE put the pharmaceutical industry at a disadvantage by not revealing how it came to its conclusions.

²⁷⁹⁶ With various levels of evidence for efficacy. A few cases may show marked deterioration when these drugs are stopped.

²⁷⁹⁷ Muscle weakness due to cholinesterase inhibitors can compromise breathing in susceptible individuals.

²⁷⁹⁸ The incidence of cardiovascular events with these agents is low and serious events are rare. (Rowland et al, 2007) Vigilance is required and intervention depends on the degree of slowing of pulse, clinical effects like syncope, and specialist opinion on the cause (e.g. one might use the drug if the problem was not due to the drug or a pacemaker is fitted).

²⁷⁹⁹ Autoimmune granulomatous hepatitis.

²⁸⁰⁰ Howard et al (2007) donepezil does not reduce agitation in AD.

²⁸⁰¹ Exelon is available as Hard Capsules (1.5 mg, 3 mg, 4.5 mg, and 6 mg) and in two transdermal patch strengths: 4.6 mg/24 hrs (contains 9 mg rivastigmine, released at 4.6 mg/24 hrs) and 9.5 mg/24 hrs (contains 18 mg rivastigmine, released at 9.5 mg/24 hrs). Only ONE patch to be applied daily: remove yesterday's patch first! Overdose (> 1 patch) may cause nausea, vomiting, hypertension, hallucinations, bradycardia, and syncope. Do not use same site during any 14-day period to avoid irritation. Start with 4.6 mg/day patch and (if tolerated and if required) increase to 9.5 mg/day patch after at least FOUR WEEKS has elapsed.

severe hepatic impairment. There may be associated weight loss²⁸⁰². Problems include nausea, vomiting, cholinomimesis²⁸⁰³, increased gastric acid secretion, and worsening of urinary obstruction or seizure disorders. Care should be taken in asthmatic patients or those with obstructive lung disease. Rivastigmine may increase the effects of succinylcholine-type muscle relaxants. It should not be given with cholinomimetic drugs and it may interfere with the action of anticholinergic drugs. It can cause asthenia, anorexia, dizziness, and tiredness. Other side effects include abdominal pain, agitation, (Ballard ea, 2005) confusion, depression, diarrhoea, dyspepsia, headache, insomnia, sweating, malaise, tremor, and an increased likelihood of upper respiratory tract and urinary infection. Rare associations are angina, GIT bleeding, and syncope. Massive overdose warrants atropine administration. Return to baseline enzyme levels takes 9 hours. Emre ea (2004) used rivastigmine for mild to moderate dementia associated with Parkinson's disease and found a moderate improvement in dementia but with increased rates of nausea, vomiting, and tremor compared to placebo-treated cases. Peak rivastigmine plasma level is reached in 60 minutes, only 40% is plasma protein bound, it readily crosses the blood-brain barrier, the plasma half-life is one hour only, unchanged drug is not found in the urine²⁸⁰⁴, the drug does not accumulate, old age does not influence bioavailability, and there is no change in Cmax and AUC in severe renal impairment. Rivastigmine is almost totally independent of the hepatic cytochrome P450 system.

(d) *Metrifonate* was a non-hepatotoxic organophosphate antischistosomal drug marketed as an acetylcholinesterase inhibitor for 'mild to moderate' AD. It is its metabolite 2,2-dichlorovinyl dimethylphosphate²⁸⁰⁵ that is the enzyme inhibitor. It was withdrawn because it caused myasthenia and respiratory muscle weakness. (De Deyn, 2002)

(e) *Galantamine*²⁸⁰⁶ (Reminyl; Reminyl XL contains prolonged release galantamine), reversibly and competitively inhibits acetylcholinesterase and enhances the response of nicotine receptors to Ach. It appears to be well tolerated and has been shown reduce both behavioural disturbance in patients and distress in carers. (Cummings ea, 2004) Galantamine does not help people with mild cognitive impairment and it may be associated with an increased mortality rate in such cases. Therefore its use is strictly confined to 'mild to severe' dementia of the Alzheimer type. Lower doses are indicated if there is moderate hepatic impairment. Avoid drug in presence of severe renal/liver impairment. Precautions: cerebrovascular disease, GIT obstructive disorders/surgery, seizures, severe asthma/COPD, urinary obstruction/bladder surgery, allergy to E110, and galactose intolerance. Interactions: other cholinomimetics, beta-blockers, digoxin, anaesthetics, CYP2D6 or DYP3A4 inhibitors. Avoid in pregnancy/lactation. Side effects: nausea, vomiting, diarrhoea, abdominal discomfort, headache, dizziness, somnolence, weight loss, confusion, falls, injury, insomnia, rhinitis, and UTI. Less common are tremor, fainting, and severe bradycardia. Atropine is given for severe overdose.

Memantine (Ebixa [Nemanda in US]), a weak non-competitive NMDA receptor antagonist²⁸⁰⁷, is indicated for 'moderate to severe' AD²⁸⁰⁸. (Foster, 2003, p. 1059) It may protect the brain against excess glutamate and to improve activities of daily living, memory, thought processes, and global function. (Reisberg ea, 2003) These effects may be less than robust. (Anonymous, 2003b) Memantine is mainly excreted unchanged by the kidneys. Hydrochlorothiazide may alter memantine excretion. A raised urine pH may increase memantine plasma levels. Memantine should be avoided with severe renal impairment and caution should be exercised in cases of epilepsy. Other NMDA antagonists²⁸⁰⁹ should not be taken concomitantly with memantine but it can be combined with cholinesterase inhibitors. Memantine may exaggerate the effects of L-DOPA, dopaminergic agonists, and anticholinergic drugs. Effects of barbiturates and antipsychotic drugs may be diminished. Uncommonly, memantine may cause hallucinations, confusion,

²⁸⁰² Weigh patient at intervals.

²⁸⁰³ Causing difficulties in the case of sick sinus syndrome or heart block.

²⁸⁰⁴ The decarbamylated metabolite is found in urine.

²⁸⁰⁵ DDVP or dichlorvos – produced by hydrolysis.

²⁸⁰⁶ A tertiary amine, phenanthrene derivative (from bulbs and flowers of snowdrops); tablets or oral solution (4 mg/ml) – 4 mg b.i.d. four at least 4 weeks, then 8 mg b.i.d. for at least 4 weeks, and finally the maintenance dose of 12 mg b.i.d.

²⁸⁰⁷ The drug dissociates rapidly from receptor if the receptor is physiologically activated, but blocks receptor when it is activated continually and moderately. It has been in use in German neurology since the 1980s.

²⁸⁰⁸ MMSE score 5-15. NICE recommended that memantine only be used as part of well-designed clinical studies, but it can be continued if the patient responds, i.e. NICE did not recommend memantine as a treatment. (Bayer, 2007)

²⁸⁰⁹ E.g. amantadine, ketamine, dextromethorphan.

dizziness, headache, or tiredness, and, less often, hypertonic muscles, vomiting, cystitis, and increased sexual drive. It comes as a tablet (10 mg) and as a solution. The starting dose is 5 mg (half a tablet) per day; each week the daily dose is increased by 5 mg; and the recommended maintenance dose is 20 mg per day²⁸¹⁰.

Combined memantine added to donepezil may produce increased gains in terms of global outcome, activities of daily living, behaviour, and cognition.(Tariot ea, 2004) Memantine improves behavioural symptoms in moderate to severe AD, especially agitation and aggression.(Gauthier ea, 2005)

*Angiotensin receptor blockers*²⁸¹¹ (Li ea, 2010) might have a role in reducing the risk for dementia or in delaying nursing home entry, although research in this area is at an early stage and not without methodological problems.

Methylthionium chloride (Rember), a blue dye used in laboratory experiments, targets clumps of Tau in the brain and is being tested in the treatment of AD wherein it demonstrated a tendency to slow disease progress.

Dimebon is a non-selective antihistamine and has been shown in Russia to improve cognition in AD.(Doody ea, 2008) It was well tolerated, the main side effects being dry mouth and low mood.

Phytoneuropsychotropics (herbal products) include ginkgo biloba and huperzine-A.²⁸¹² Huperzine-A has been employed for centuries in China. It seems to have acetylcholinesterase activity but with little effect on butylcholinesterase. There is some evidence of efficacy when used alone or in combination with ginkgo biloba. However, DeKosky ea (2008) assigned 3,069 community volunteers aged at least 75 years with either normal cognition or mild cognitive impairment to either placebo or ginkgo biloba 120 mg twice daily and followed them up for a median of 6.1 years and found no reduction in either overall dementia or AD rates. Whilst the vinca alkaloid vinpocetine improves learning and memory in animals it does not benefit dementia sufferers.

The common sage (*Salvia officinalis*²⁸¹³) might be helpful for agitation.(Akhondzadeh ea, 2003)

New treatment concepts include selective inhibition or modulation of beta- and gamma-secretase activity.

A number of secretases are involved in beta-amyloid peptide (40-42 amino acids) production from amyloid precursor protein. Normally, APP is cleaved by beta-secretase and then by alpha-secretase with no A β accumulation. However, in AD it appears that γ -secretase (rather than alpha-secretase) cleaves much of APP leading to a 42-amino acid important in accumulation of amyloid. R-flurbiprofen, a gamma-secretase modulator, leads to shorter amino acids that do not lead to A β accumulation.

Hypercholesterolaemia accelerates amyloid pathology and reduced cholesterol intake slows plaque development in transgenic mouse models, a finding that may have some application in humans²⁸¹⁴. Statins²⁸¹⁵, by reducing cholesterol, have been suggested as having some therapeutic role. However, because more educated people may be more likely to take such drugs, the effects of education have to be controlled for in research. Also, Zandi ea (2005) found no support for a preventive role for statins. Nerve growth factor²⁸¹⁶, a neurotrophin, and deprenyl, a MAO-B inhibitor, have long been suggested as possible neuroprotective agents. Ampakines, the subject of research, attach to AMPA receptors and normalise glutamate activity; they also increase nerve growth factor (NGF) production. Gene therapy, implanting

²⁸¹⁰ This may be given once-daily.

²⁸¹¹ These are antihypertensives and not the same as ACE inhibitors.

²⁸¹² None of these are first line treatments. *Ginkgo biloba*, from the leaves of the maidenhair tree, was used in Chinese medicine for millennia; concerns have been raised over a tendency to cause bleeding. It can also cause GIT upset and headache.

²⁸¹³ A small evergreen shrub used as a food flavour. *Salvia* (sage) is Latin for 'to heal'. The 'essential oil' contains cineole, borneol and thujone and the leaf contains many chemicals such as oleic and tannic acids. The shrub has been touted as a treatment for many ills.

²⁸¹⁴ Amyloid deposition in blood vessel walls in AD is often harmless but not always so. There may be thrombosis of leptomeningeal or cortical vessels leading to many small infarcts. There may be ischaemic changes in the white matter. Bleeding of various degrees may occur into brain or subarachnoid space. Unlike in hypertension, which tends to affect the basal ganglia, the bleeding in AD tends to be peripherally placed.

²⁸¹⁵ Statins (e.g. simvastatin) have been associated with sleep problems, memory difficulties, depressed mood, sexual dysfunction, and interstitial lung disease.

²⁸¹⁶ Genetically modified fibroblasts that produce have been transplanted into brain NGF with some positive effect on cognition.(Tuszynski ea, 2005)

modified cells into the AD brain where they produce NGF, is in its early stages of development. The possibility of immunising people against AD requires further research.

Lithium inhibits glycogen synthase kinase-3 (involved in APP metabolism and tau phosphorylation). There is evidence for an increased risk for dementia in people with affective disorders (e.g. Thompson ea, 2005) and some evidence that lithium may reduce this risk.(see Nunes ea, 2007; Kessing ea, 2008)

Do not use antipsychotics as a convenient replacement for good care, to satisfy the needs of a care home over the clinical requirements of patients. Staffing levels in such settings are often poor²⁸¹⁷. The *Omnibus Budget Reconciliation Act of 1987* (aka OBRA 87) in the USA placed restrictions on such prescribing with inconsistent results.(Denning & Milne, 2008, p. 362) Schneider ea (2005) conducted a meta-analysis of the literature and found that atypical antipsychotic use was associated with a small increase in mortality in elderly demented compared to placebo. Most studies were of short duration, they were more often unpublished, and they were usually funded by the pharmaceutical industry. Schneider ea (2006) found adverse effects of atypical antipsychotic drugs for treatment of psychosis, aggression, or agitation in Alzheimer patients outweighed any therapeutic advantages. Sultzer ea (2008) used antipsychotic drugs for psychosis or agitated/aggressive behaviour in outpatients with Alzheimer's disease: the drugs were useful for certain symptoms (e.g. anger, aggression, paranoid thinking) but did nothing for functional status, care requirements, or quality of life. Conventional antipsychotic drugs may carry similar risks for mortality when used in demented subjects.(Kales ea, 2007) The decision to prescribe antipsychotic drugs to demented patients should ideally follow failure of other approaches, consultation, and monitoring.(Anonymous, 2007c; O'Brien, 2008) APA Practice Guidelines (2007) suggest caution in their use at the lowest effective dosage, education of patients and families about potential risks and benefits (especially mortality risk), and choice of particular drug based on side effect profile and individual patient characteristics. The effects of antipsychotic drugs on weight and cholesterol cannot be ignored in AD patients.(Zheng ea, 2009) Haw ea (2009) found that all British old age psychiatrists (only 31% response rate) still used antipsychotic symptoms for behavioural and psychological symptoms of dementia (BPSD) and were not particularly impressed by NICE guidelines on the subject! Burns and Iliffe (2009a) suggest using trazodone²⁸¹⁸, clomethiazole, and SSRIs²⁸¹⁹ for agitation in dementia.

ECT (Sutor & Rasmussen, 2008) has been used safely and effectively for agitation in AD.

Women have been at the forefront in starting up self-help national organisations.(O'Shea, 1992) Reality orientation therapy should be individualised and non-confrontational. Otherwise it may lead to anger, frustration, and depression.(Simard & Sampson, 2008, p. 237)

Lewy body dementia (LBD)²⁸²⁰

Lewy bodies are inclusion bodies containing abnormally phosphorylated neurofilament proteins aggregated with ubiquitin²⁸²¹ and alpha-synuclein. They can be of various shapes and even be outside the cell. In the substantia nigra they are brightly eosinophilic (pink) with hyaline core and paler halo; in cortex they are faintly eosinophilic and have no core. They were considered confined to idiopathic Parkinson's disease (paralysis agitans) until recent years.²⁸²²

'Pure' LBD (with no AD pathology), although reported (Gurd ea, 2000), is rare. McKeith (2002) and Rapoport ea (2008, p. 251) admit that the boundary between LBD and Parkinson's disease with

²⁸¹⁷ There is no point in educating care home staff if the lessons do not become part of the culture of the facility; staff turnover alone will cause atrophy of skills unless managers are involved in training.(Denning & Milne, 2008, p. 364)

²⁸¹⁸ Trazodone is suggested as being useful in the control of screaming.

²⁸¹⁹ Paroxetine is more anticholinergic than other SSRIs.

²⁸²⁰ This is also known as dementia with Lewy bodies (DLB), dementia of the Lewy body type, diffuse Lewy body disease, and cortical Lewy body disease. The general term LBD includes 'common form LBD' (or 'Lewy body variant' = Lewy bodies + AD pathology) and 'pure form LBD' (or 'diffuse LBD' = Lewy bodies minus AD pathology). Friedrich Heinrich Levy (1885-1950) discovered these bodies in the brains of Parkinson's disease patients in 1912 when with Alzheimer at Kraepelin's Royal Psychiatric Clinic in Munich. When he moved to the US he changed his name to Frederic Lewy.

²⁸²¹ Ubiquitin is a protein that targets other proteins for degradation by the proteasome.

²⁸²² Based on postmortem work (Lewy bodies in cerebral cortex and substantia nigra, may have senile plaques but no tangles, widespread reduction in level of choline acetyltransferase in neocortex, and some reduction in DA levels in caudate nucleus), it is often stated that LBD cases (11-25%: Wilcock, 2003) may constitute the second or third commonest cause of dementia [after AD (52%) and vascular dementia], although some, but not all, authors wonder about its nosological status and wonder if it is a variant of AD.(Carter & Levy, 1995; Miller, 1997; Nixon & Albert, 1999; Foster ea, 2003, p. 1052) Others point out that AD and LBD frequently or usually coexist (Foster, 2003, p. 1061; Falk ea, 2004, p. 139) and Wise and Rundell (2005, p. 50) point out that the relative frequency of LBD versus vascular dementia depends on the author one is quoting! Bennett ea (2006) prospectively reported that 7-14% of non-demented/non-cognitively impaired people who died had Lewy body pathology.

dementia/psychosis remains indistinct. Indeed, there is generally some overlap in the distribution of Lewy bodies between LBD and paralysis agitans, (Olichney ea, 1995; Foster, 2003, p. 1051) some Lewy bodies being present in the cortex in idiopathic Parkinson's disease and many patients with LBD meet the pathology criteria for AD, (Cras, 2002; Lovestone, 2002, p. 289) such as Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria. Lewy bodies contain ubiquitin and alpha-synuclein²⁸²³ and antibodies to these proteins can be used in postmortem tissue as a method of detecting these bodies. The dose of alpha-synuclein (number of genes) may play a role in the aetiology of dementia. Lewy bodies in autonomic ganglia may be associated with postural hypotension. Lewy neurites are diffusely aggregated neurofilament proteins found particularly in the CA2-3 region of the hippocampus in LBD. In Parkinson's disease up to 70% of cells are lost from the substantia nigra before symptoms manifest themselves. In LBD up to 40% of the same cells are lost, which may explain the vulnerability of such cases to EPS when given neuroleptic medication. Functional neuroimaging (PET, SPECT) early in the course of LBD may show reduced occipito-temporal cortical activity, with much wider involvement later²⁸²⁴. There may be an excess of males. (Weiner ea, 1996)

Dementia with Lewy bodies neuropathology

Lewy bodies

Lewy neuritis

Neuritic (senile) plaques

Neurofibrillary tangles

Regional neuronal loss²⁸²⁵

Microvacuolation (spongiform)

Loss of synapses

Note: LBD is more or less indistinguishable pathologically from Parkinson's disease-associated dementia (PDD) but PDD responds to L-DOPA from the start and there is delayed onset of dementia (>12 months) whereas Parkinsonism develops late in LBD and, in almost one-third of cases, may not develop at all

Clinical features of LBD include marked fluctuations in cognitive impairment, amnesia, apraxia, aphasia, EPS, falls (orthostatic hypotension), clouding of consciousness, visual and auditory hallucinations²⁸²⁶, paranoid delusions²⁸²⁷, and hypersensitivity to the adverse effects of neuroleptic drugs, including atypicals. The excess psychotic symptoms may relate to reduced DA turnover and metabolism that is reflected in lower CSF HVA levels. Olfaction is impaired. Cognitive decline has correlated with both neuroleptic usage and with persecutory ideas! (McShane ea, 1997) Vivid dreams are often reported in DLB and REM-sleep behaviour disorder is common in DLB and may long precede it. (Ericksen & Tsuang, 2007, p. 477) Anticholinergic drugs may precipitate life-threatening delirium. (Miller, 1997) The course followed by LBD varies between patients but is more rapid than with AD and death occurs about six years following diagnosis.

The psychopathology of LBD (delusions and hallucinations) may be ameliorated by the anticholinesterase rivastigmine. (McKeith ea, 2000) Poor light (e.g. evening) and patterned furnishings may exacerbate hallucinations and attention should be aimed at remedying such matters. L-deprenyl has been suggested for Parkinsonism but it may precipitate hallucinations. Antidepressants with orthostatic propensities are best avoided. Atypical antipsychotic drugs may cause as many problems do as typical agents, although olanzapine, quetiapine, aripiprazole or clozapine may be useful. (e.g. Fernandez ea, 2003) BZDs have been suggested for behavioural problems and restless or wandering behaviour may respond to beta-blockers or L-DOPA. The following box presents further research details.

²⁸²³ With disorders such as multiple system atrophy and Parkinson's disease, LBD is included in the family of α -synucleinopathies.

²⁸²⁴ There may be sparing of the primary sensorimotor cortex.

²⁸²⁵ Nucleus basalis of Meynert and brain stem are commonly affected.

²⁸²⁶ Insight into the pathological nature of hallucinations may be preserved for long periods. Visual hallucinations, present in at least 60% of cases, may relate to a reduction in ACh (greater than in Parkinson's disease with dementia) and relative sparing of 5-HT. (Perry ea, 1990) Visual hallucinations may respond to cholinesterase inhibitors. The usual visual hallucinations are of people or animals that may disappear when the patient stares at the image. Other visual hallucinations may be of smoke, fire, or water lying on a surface. Also, the patient may see (illusions) things such as a face in detailed objects like a bush.

²⁸²⁷ Delusions may stem from up-regulated postsynaptic muscarinic receptors.

Summarised research on Lewy body dementia (LBD)

1912. The German neuropathologist Friedrich Heinrich Lewy (1885-1950), while working with Alzheimer, described spherical neuronal inclusions.

1986. Parkinson's disease patients with overt dementia are no more often depressed than in those without dementia.

1990. Anergia, motor retardation, and early awakening may be equally severe in Parkinson's disease patients with and without depression.

1997. LBD may resemble AD except for better recall and worse praxis in the former.

A mutation of the gene for α -synuclein on chromosome 4 is associated with rare, autosomal dominant, early-onset Parkinson's disease.

1999. Olanzapine had little advantage over conventional agents.

Non-significant neurone loss in cortical areas affected by Lewy bodies (perhaps synaptic dysfunction is operative?)

2000. Apathy, anxiety, delusions and hallucinations reduced more in LBD than in controls by rivastigmine, better if dose titrated for individual.

Olanzapine used for BPSD and psychosis in dementia was safe (somnia and gait disturbance reported) and effective at 5-10 mg/day, but 15 mg/day was ineffective and associated with significant peripheral anticholinergic effects.

2001. Occipital hypometabolism is seen in LBD both with and without co-existing AD pathology.

Frequency of co-occurring AD and LBD pathological stigmata is greater than that due to chance.

2003. Substantial relief of depression from ECT in a series of 7 cases.

2004. Olanzapine indication in dementia terminated because of reports of increased mortality and stroke in that group.

2008. 123 I-FP-CIT SPECT²⁸²⁸ improves diagnostic accuracy of LBD – if scan is abnormal in a possible case of LBD it favours a diagnosis of that disorder.

Vascular dementias²⁸²⁹

Vascular contributions to dementia are easier to identify today because of FLAIR²⁸³⁰ and other MRI techniques. Fresh infarcts can be identified with diffusion-weighted MRI. The occipito-frontal power ratio is higher in dementia due to a vascular cause than in cases of AD. Also, EEG coherence will be decreased between areas disconnected²⁸³¹ by vascular lesions. Larson (1993) listed the risk factors for vascular dementia as old age, high blood pressure, smoking, diabetes mellitus²⁸³², cardiac disorders, atrial fibrillation, and extracranial arterial disease. To these can be added male sex. A twin study from Norway

²⁸²⁸ [123 I]-2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl)nortropane.

²⁸²⁹ Vascular dementia is reportedly more common in AD in Japan, among Blacks and in at least one unselected elderly Swedish group. (Skog et al, 1993) AD may be becoming more common in Japan, and more so in Japanese-Americans in Seattle. (Homma, 2000) Fratiglioni et al (2008, p. 392) are critical of reports of an excess of vascular dementia in East Asia. Stewart (2002) is sceptical about the usefulness of vascular dementia as a diagnostic category because it involves a high degree of subjective judgement, because it subsumes many different disorders, and because it overlaps with AD. Again, Stewart (2008) lists problems with the diagnosis as (a) stepwise vs gradual course poorly predicts pathology; (b) post-stroke dementia may occur gradually, often without further infarction; (c) risk factors for stroke may also be risk factors for AD; (d) dementia from cerebrovascular disease is usually associated with Alzheimer pathology; (e) research diagnostic criteria poorly predict pathology; (f) poor inter-rater reliability of clinical diagnostic criteria for vascular dementia; (g) operational definitions of dementia tend to ignore the common non-memory deficits (e.g. executive) found in vascular cases. A systematic review and meta-analysis (DeBette & Markus, 2010) concluded that white matter hyperintensities (*leucoariosis*) on brain MRI were associated with increased risk of CVA, cognitive decline, dementia, and demise. There was much heterogeneity in the way such lesions were measured and analysed and some studies were omitted because of use of different scales that viewed white matter hyperintensities as continuous variables.

The **Hachinski ischaemic index (HII)** was introduced in the 1970s. The higher the score the more likely dementia is due to cerebrovascular disease. Scores (in brackets) are given for abrupt onset (2), stepwise deterioration (1), fluctuating course (2), nocturnal confusion (1), relative preservation of personality (1), depression (1), somatic complaints (1), emotional incontinence (1), history of hypertension (1) or strokes (2), evidence of associated atherosclerosis (1), and focal neurological symptoms (2) or signs (2). A score of < 4: probable AD; 4-7: probable mixed AD and multi-infarct dementia (MID); > 7: probable MID. The HII was derived from patients who were relatively young and mildly impaired. The Index does not take account of imaging findings and are of diminished applicability in cases of insidious onset. For these reasons is used less today than heretofore.

The **NINDS-AIREN** (National Institute of Neurological Disorders and Stroke – *Association Internationale pour la Recherche et l'Enseignement en Neurosciences*) criteria of 1993 avoid (highly specific but of low sensitivity) avoid trying to define mixed AD-vascular dementia. *Probable vascular dementia* = early onset of abnormal gait (magnetic, *marche à petit pas*, apraxic-ataxic, or parkinsonian), unsteady/prone to falling, early onset of urinary incontinence, pseudobulbar palsy (dysphagia, dysarthria, emotional incontinence), changes in mood and personality, and psychomotor retardation, perseveration, and difficulty shifting/maintain sets.

Definite vascular dementia = clinical criteria for probable case, biopsy/autopsy histology favours cerebrovascular disease, plaques/tangles do not exceed what would be expected at patient's age, and no other cause of dementia.

²⁸³⁰ Fluid-attenuated inversion recovery sequences.

²⁸³¹ Disruption of cortico-cortical and cortico-subcortical fibres.

²⁸³² There is some evidence that diabetes mellitus, especially type II, increases the risk of vascular dementia (and, to a lesser extent Alzheimer's disease). No association between decline in cognitive function and frequency of severe hypoglycaemia has been found, but high mean glycated haemoglobin concentration and a moderate decline in motor speed and psychomotor deficiency has been reported. There are many possible mechanisms involved (ranging from genes to hypertension and vascular pathology). (Strachan et al, 2008)

suggested that heredity may be far less important in the genesis of vascular dementia than in AD.(Bergem ea, 1997) Vascular dementia is an umbrella term covering all dementias due to vascular disease, multi-infarct cases being but one example. There is no specific treatment. Blood pressure should be controlled²⁸³³, low dose aspirin might help²⁸³⁴, and there may be a role for surgical correction of carotid artery stenosis. Depression seems to be more common in vascular dementia than in AD.(Allen & Burns, 1995) Antidepressants, especially SSRIs, can be used to treat or prevent post-stroke depression and they may improve cerebral recovery and improve long-term survival. Antidepressants may be augmented with calcium channel blockers, such as the centrally active nimodipine, in post-stroke depression. *Multi-infarct dementia*²⁸³⁵ tends to vary in severity over time. Each new lesion adds to the total cognitive disability. The patient often retains insight. Irritability and depression²⁸³⁶ are commonly encountered. The mortality rate is lower than for AD. Epilepsy (20%), hypertension, transient ischaemic attacks (TIA²⁸³⁷), and renal, ophthalmic or cardiac disease may complicate the picture. It is more common in males. Atheroma of some degree is common within the cerebral circulation in the senium. However, extreme degrees of atherosclerosis in the postmortem specimen are quite compatible with clinically normal cognitive functioning.

Pathology in vascular dementia

Lenticulostriate branches of middle cerebral artery most often affected

Vasculature progressively narrows, bloats, twists, and becomes yellow and rigid

Supple vessels give way to corrugated drainpipes

Brain parenchyma may be normal, cystic, infarcted, necrotic, or scarred

Dementia is due to cerebral softening from multiple small infarctions²⁸³⁸ of brain tissue - it is not the cerebral arteriosclerosis *per se* that causes dementia

Middle cerebral artery most often involved

Followed by **posterior** artery supplying areas important for memory, e.g. the hippocampus

Anterior cerebral artery least often affected

According to some authorities (Korczyn, 2002) pure Alzheimer and vascular dementias are rare and mixed pathology has been underestimated

Strategic infarct

An infarct that, because of its position (e.g. hippocampus), causes dysfunction out of proportion to its size

E.g. Severe memory problems due to bilateral paramedian thalamic or fornical infarction; severe problems with comprehension following left supramarginal or angular gyrus infarction

Acute stroke can be treated with IV tissue plasminogen activator (within 3 hours) or aspirin (within 2 days) and decompression surgery. Preventive measures for stroke include anti-platelet, anti-hypertensive and anti-coagulant medications, cholesterol reduction, and endarterectomy.(Donnan ea, 2008)

²⁸³³ However, blood pressure may fall with the onset of dementia, prompting a review of antihypertensive treatment.(e.g. Pettiti ea, 2005)

²⁸³⁴ Kang ea (2007) found that low dose aspirin failed to improve cognition in healthy older females. Price ea (2008) found low dose aspirin not to affect cognitive function in middle aged to elderly people at moderately increased cardiovascular risk. Methodological issues remain a problem.(Whalley & Mowat, 2007) Simard and Sampson (2008, p. 236) point out that results of studies of NSAIDs are 'widely' contradictory and there are 'serious concerns about tolerability'. However, aspirin does prevent major vascular events.(Eikelboom & O'Donnell, 2008)

²⁸³⁵ Vladimir Hachinski and colleagues proposed the term *multi-infarct dementia* in 1974.

²⁸³⁶ Depression may be obstinately persistent.

²⁸³⁷ **TIA**s were defined as acute phenomena (focal cerebral or monocular deficits, the latter being due to ischaemia of the retina) that resolve within 24 hours. We know that any such attack lasting more than 4 hours can cause infarction and thrombolytic therapy should be given with the first 3 hours. A more modern definition is one that limits the event to 1 hour with no evidence (on diffusion-weighted MRI) of infarction. TIAs are not benign because they are associated with increased short-term morbidity and mortality. *Crescendo TIAs* consist of > 3 TIAs in a 3 day period during which the attacks become more severe and increase in frequency and duration.

²⁸³⁸ **Lacunar infarcts** are small punctuate lesions (< 1.5 cm in diameter) that often affect deep white matter, basal ganglia and brainstem: many such lacunae (or fewer large strokes) can cause multi-infarct dementia. The patient may have a history of CVAs or MIs. High blood pressure is a major predisposing factor. The presence of lacunes plus depression in the elderly is associated with significant reduction in life expectancy.(Lavretsky ea, 2010)

*Binswanger's disease*²⁸³⁹

Rare variant of cerebrovascular disease of controversial nosological status

Starts in middle to old age

Periventricular and deep white matter bear brunt of pathology

Atherosclerotic changes occur in local nutrient arteries leading to many small white matter infarctions, the cortex being spared

CT scan shows periventricular lucency

MRI scan shows areas of decreased and increased signal intensity on T1- and T2-weighted images respectively (Such lesions must be distinguished from the smoother periventricular caps and rims and from 'unidentified bright objects' or UBOs, which are normal variants)

Clinical picture includes progressive dementia with generalised slowing of intellectual processes, memory impairment, and disorientation, and (but not in all cases) neurological signs

May also get depression, euphoria, irritability and anxiety

Anti-phospholipid antibody syndrome (Hughes' syndrome) (D'Cruz ea, 2007; Cohen ea, 2010)

Described in 1983

Recurrent arterial and venous (including renal vein/renal infarction) thromboses

Kidney – above plus thrombotic microangiopathy, antiphospholipid syndrome nephropathy

Heart valve disease, coronary artery disease, pulmonary embolism

Recurrent early miscarriage/intrauterine fetal death²⁸⁴⁰; early/severe pre-eclampsia

May experience TIAs, CVAs and multi-infarct-like dementia

Migraine

Skin - livedo reticularis, Raynaud's phenomenon

Overlaps with SLE

*CADASIL*²⁸⁴¹

Prevalence of 1/50,000

Familial disorder associated with autosomal dominant (variable penetrance) gene at 19p13²⁸⁴²

Mutation in Notch 3 gene²⁸⁴³

Phenotype varies, even within a family

Walls of small and medium penetrating arteries thickened and fibrotic²⁸⁴⁴

A white matter ischaemic disease

60-70% decrease in cortical choline acetyltransferase

Parieto-occipital and dorso-frontal axonal damage

Immuno-staining of skin biopsy may assist in diagnosis: granular osmophilic material

Arteriolar smooth muscle shows GOM (glomerular osmophilic material) on electron microscopy

Adults²⁸⁴⁵ with no vascular risk factors develop vascular dementia and pseudobulbar palsy (dysphagia, dysarthria, and emotional incontinence)

Youngsters may develop migraine and depression with TIA and CVA in 20s and 30s, and dementia in their 50s

May present with psychosis, mania, or depression

Duration about 10 years

Address stroke risk factors²⁸⁴⁶

²⁸³⁹ Subcortical arteriosclerotic (or vascular) encephalopathy: It is an extreme form of 'small vessel disease' (diffuse and widespread), itself a cause of subcortical dementia. The effects of small vessel disease may be added to those of lacunar infarcts.

²⁸⁴⁰ 27% of women with at least 2 spontaneous miscarriages have antiphospholipid syndrome.

²⁸⁴¹ Cerebral dominant arteriopathy with subcortical infarcts and leucoencephalopathy, formerly hereditary multi-infarct dementia.

²⁸⁴² Related to another chromosome 19 gene, this time for familial hemiplegic migraine.

²⁸⁴³ Notch 3 at 19p13.1 encodes a transmembrane receptor with an important function in vascular smooth muscle signalling pathways. There are 33 exons. Distribution of gene mutations varies between countries.

²⁸⁴⁴ The problem lies in the basal smooth muscle cells.

²⁸⁴⁵ Mean age of onset = 35-40, age range 20-70. (Taylor & Doody, 2008)

SSRIs for depression

*Fabry's disease*²⁸⁴⁷

Painful neuropathy and progressive involvement of cardio- and cerebro-vascular systems and kidneys

*HERNS*²⁸⁴⁸

Autosomal dominant disorder with basement membrane involvement

Anton's syndrome (cortical blindness)

Inability to perceive visual stimuli (cannot see) because of bilateral cortical damage²⁸⁴⁹ with normal eyes and pupils²⁸⁵⁰ Patients **deny blindness**, confabulate, and describe vividly what is 'seen'

Often already have cognitive impairment, visual loss, and mainly nondominant hemisphere damage

Rarely, despite cortical blindness, visual stimuli may evoke responses (**blindsight**) which may be due to subcortical/brainstem processing of perceptions – direct projections from the lateral geniculate nucleus to the extrastriate cortex may contribute to blindsight (Schmid ea, 2010)

Aetiology includes Alzheimer's disease, vascular lesions, Creutzfeldt-Jakob disease, lissencephaly, and carbon monoxide poisoning

Normal pressure hydrocephalus²⁸⁵¹

The essential features are normal CSF pressure²⁸⁵² and communicating hydrocephalus²⁸⁵³. Stretching of nerve fibres appears to be important in the production of clinical manifestations. Memory problems develop over many weeks, there is psychomotor retardation, and the first signs are often gait apraxia (e.g. 'magnetic' gait: unable to lift feet in order to commence walking) and urinary incontinence. Headache is uncommon. Pyramidal or other long tract signs may dominate the clinical picture whereas other cases may present as a cerebellar syndrome with, e.g., intention tremor. Other cases are simply demented. Combined pictures may occur.²⁸⁵⁴ Air-encephalography and isotope-encephalography were commonly used to assist diagnosis. The air or isotope concentrated in the dilated ventricles and failed to reach the convexity of the hemispheres. CT is used today and shows symmetrically enlarged ventricles²⁸⁵⁵ without significant cerebral atrophy, i.e. dilatation of ventricles is out of proportion to widening of sulci. SPECT shows a reduced cerebral blood flow, especially (unlike AD) in the anterior brain.

Sometimes there is a history of meningitis, subarachnoid haemorrhage, and intracranial (posterior fossa) surgery or head injury. Other associations include distortion of the third ventricle by the basilar artery in hypertensives, aqueduct stenosis, and tumours of the posterior fossa.

A shunt²⁸⁵⁶ (better outlook if periods of raised CSF pressure can be demonstrated) that runs from a cerebral ventricle to the right atrium or to the peritoneum may benefit a proportion of cases²⁸⁵⁷, gait difficulties

²⁸⁴⁶ Antiplatelet therapy (aspirin, dipyridamole), antihypertensives, statins (even with normal cholesterol levels), treatment for diabetes, decrease weight, stop smoking, exercise, moderate alcohol intake, and treat any co-morbid problems such as valvular disease. (Taylor & Doody, 2008)

²⁸⁴⁷ X-linked recessive lysosomal storage disorder: deficiency of alpha-galactosidase A with accumulation of globotriaosylceramide intracellularly: mainly middle-aged men but female carriers at risk of stroke.

²⁸⁴⁸ Hereditary endotheliopathy with retinopathy, nephropathy and stroke – generalised vasculopathy in Chinese Americans.

²⁸⁴⁹ E.g. due to occlusion of the posterior cerebral arteries, multiple sclerosis, or head trauma.

²⁸⁵⁰ Extensive damage to occipital lobes may cause cortical blindness. Unlike in peripheral causes of blindness, the fundi are normal and pupillary light reflexes are preserved.

²⁸⁵¹ *Hakim-Adams syndrome*: Raymond Adams and co-workers described this in 1965. Opinion has varied over the years on its frequency, some modern authorities suggesting that it is a very rare cause of dementia. (Foster, 2003, p. 1054)

²⁸⁵² In fact, intermittently raised pressure (B waves), especially at night, are found when continuously monitored.

²⁸⁵³ There is no block in ventricles but there is a block in the subarachnoid space. CSF gets out of the ventricles but cannot flow up over the hemispheric surfaces.

²⁸⁵⁴ Vascular dementia, it should be noted, is a more common cause of subcortical dementia, gait disturbance, and urinary incontinence, than is normal pressure hydrocephalus.

²⁸⁵⁵ *Evan's ratio* = greatest width of frontal horns of lateral ventricles/maximum internal width of skull. A ratio of > 0.3 suggests significant ventriculomegaly. In cases in which such ventriculomegaly is associated with severe cortical atrophy or widespread cerebrovascular disease the ventriculomegaly may just be due to loss of brain tissue rather than normal pressure hydrocephalus.

²⁸⁵⁶ Various further investigations will be performed prior to shunting: assessing cognition before and after removing CSF, slow prolonged removal of CSF by lumbar catheter, 24-hour intracranial pressure monitoring, and saline infusion into

responding best; the milder the dementia the better the chance of an improvement. With use of adjustable valves with subcutaneous magnetically controlled mechanisms to allow manipulation of CSF drainage by the clinician the patient must avoid magnets, including MRI scanners.

Neurosyphilis²⁸⁵⁸

The advent of HIV has led to a resurgence of neurosyphilis. (French, 2007) There are three classic types of neurosyphilis: asymptomatic with CSF changes only, meningovascular involving the leptomeninges and blood supply, and parenchymatous with degeneration of neurones and axons. The last type includes general paresis (GPI, dementia paralytica), tabes dorsalis (locomotor ataxia), and taboparesis. There has been a shift away from parenchymatous to meningovascular syphilis over time. Atypical and attenuated presentations are now much more likely. Both GPI and meningovascular syphilis²⁸⁵⁹ may lead to dementia. Affective or personality change is common and may precede intellectual deficits. The disorder may present as a social indiscretion. Three males are affected for every female and there is a wide variation in the age of onset but the mean is around 40 years. Congenital GPI can affect the young child and GPI can start in the very old. The period between infection and onset of GPI is usually of the order of 10-15 years with wide variation²⁸⁶⁰. The following forms²⁸⁶¹ have been described: grandiose (expansive), simple dementing, depressive, taboparetic, manic, schizophrenia-like ('paraphrenic'), neurasthenic, acute brain reaction, Korsakoff-like, epileptic, miscellaneous neurological presentations, Lissauer's²⁸⁶², and juvenile. GPI is the only type of syphilis wherein *T. pallidum* can be visualised in the brain.

It is important to obtain the patient's cooperation in contact tracing and the family may need to be tested. *Treponema pallidum* cannot be cultured *in vitro* but it may be seen with dark ground microscopy. Enzyme immunoassay detects IgM and IgA antibodies. If this is positive it should be confirmed using the TPHA/TPPA and VDRL/RPR tests.²⁸⁶³ In cases of suspected neurosyphilis the CSF may need to be tested. IV aqueous benzylpenicillin 18-24 million units daily for 1-2 weeks is the recommended treatment for neurosyphilis. 2 gram of ceftriaxone given parenterally for the same period may be used if the patient is allergic to penicillin. ECT may exacerbate focal neurological signs.

Pellagra²⁸⁶⁴

subarachnoid space through a lumbar needle with continuous CSF pressure monitoring and calculation of CSF absorption. All such tests have their own problems and deficiencies.

²⁸⁵⁷ About 40%.

²⁸⁵⁸ Theories of the **origin of syphilis** vary from the Crusaders to Spanish adventures in the New World to a worldwide (including Europe) mutation at the close of the 15th century. Fracastoro gave the name syphilis to this disease in 1530. August von Wasserman introduced his blood test (WR) in 1906. The first clear accounts of general paralysis of the insane (general paresis, GPI), which causes an insidious dementia, date from 19th century Paris; it spread from there to other parts of the world; and GPI may have arisen because of a mutation in *Treponema pallidum*. (See Hare, 1998, ch. 3) Syphilis was a leading cause of insanity at the end of the nineteenth century. (Strathern, 2005, p. 332) Its more famous victims may have included Oscar Wilde, Nietzsche, Gauguin, and John Keats.

Congenital syphilis featured in the Norwegian playwright Henrik Johan Ibsen's (1828-1906) *Ghosts* (an attack on Victorian hypocrisy) in 1881. It has been suggested that *T. pallidum* underwent mutation in order to cause GPI. Fournier of Paris showed a statistical relationship between syphilis, paresis and tabes in 1894. Schaudinn of Berlin identified the causative organism in material from a genital lesion in 1905. Noguchi and Moore demonstrated *T. pallidum* in the brain of GPI patients in 1913. There was a resurgence of syphilis in Dublin and other European cities from 2000, with a peak in Irish notifications of 300 cases in 2002. The **Argyll Robertson pupil** is small, stays the same size, is unchanged by light/shade, contracts on convergence, and dilates when the patient ceases to attempt convergence. Pupil response to light is lost although accommodation to near objects is normal. Douglas Argyll Robertson (1837-1909) was born in Edinburgh and was a pupil of Remak, Romberg and von Graefe; he experimented with physostigmine in the early 1860s and observed his eponymous pupil in 1869. (Timoney & Breathnach, 2010) Elderly diabetics may have small and irregular pupils with a sluggish light reflex or even the full Argyll Robertson pupil, so-called *pseudo-tabes*.

²⁸⁵⁹ Meningovascular syphilis may present as subacute meningitis with papilloedema and cranial nerve involvement; chronic expansion of a gumma; or, if there is involvement of the cord meninges, paraparesis.

²⁸⁶⁰ About half that time applies for meningovascular syphilis. The pupils are unequal, irregular, and eccentric. There may be loss of iris pigment. Diabetes (**pseudo-tabes**) is a commoner cause today than is neurosyphilis. The lesion is probably pretelectal (midbrain).

²⁸⁶¹ The relative preponderance of different clinical presentations may have changed over time. (Hare, 1998, ch. 3)

²⁸⁶² Hemiparesis, aphasia and other evidence of focal brain damage.

²⁸⁶³ *T. pallidum* haemagglutination or particle agglutination assay (TPHA/TPPA); Venereal Disease Research Laboratory and rapid plasma reagin (VDRL/RPR) tests.

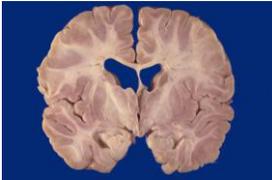
²⁸⁶⁴ *Mal de la Rosa*, described by the Spanish physician Gaspar Casal (1679-1759) in 1735, is due to nicotinic acid (vitamin B3) deficiency. Goldberg detected its more specific dietary origin in 1915 and in 1937 niacin was shown to be the deficient chemical. Niacin is found in a number of foods. Removal of bran eliminates niacin from cereals although foods in developed areas are often fortified with the vitamin. Eggs and cheese contain tryptophan. Humans can make niacin from tryptophan. Deficiency of vitamin B6 and riboflavin can give rise to pellagra because the enzymes involved in converting tryptophan to niacin (kynureninase and kynurenine hydroxylase) are dependent on these vitamins. Pellagra rarely accompanies malabsorption states. Other associations are

Pellagra, due to deficiency of nicotinic acid (niacin) or its precursor (tryptophan) is found in maize-eating areas, alcoholics, and refugees. The clinical features are dermatitis (symmetrical, affecting sun-exposed areas²⁸⁶⁵), diarrhoea (or constipation), delirium, dementia, depression, dysmnnesia, and neurasthenia, together with angular stomatitis, wasting, increased reflexes, clonus, positive Babinski sign, and peripheral neuropathy. Mild cases may be depressed, apathetic and even thought disordered. Frank psychosis may occur in severe cases. The application of epidemiological principles to the cause and treatment of pellagra provided a convincing demonstration of the public-health approach to mental illness. There is also an acute form of pellagra with delirium, rigidity and no rash.

Huntington's disease²⁸⁶⁶ (HD; O'Shea, 1997, 2003; O'Shea & Falvey, 1991)

This is inherited as a single dominant genetic trait (IT-15 gene at chromosome 4p 16.3; Gusella ea, 1983) and has a mean age of onset of 40 years (range 2-90²⁸⁶⁷) and affects the sexes equally. The actual gene was discovered by MacDonald and co-workers.(Huntington's Disease Collaborative Research Group, 1993) It may a low genetic mutation rate²⁸⁶⁸: it is thought that an unaffected father has an unstable CAG repeat sequence (cytosine-adenine-guanine) that undergoes expansion. People with HD express a 350 kDA huntingtin²⁸⁶⁹ protein containing the polyglutamine sequence translated from the (CAG)_n repeat. It has been suggested that mutant huntingtin protein may open excess channels in mitochondrial membranes with resultant loss of calcium leading to reduction in the electrical gradients needed to drive ATP synthesis. In a worm model, the length of the mutant polyglutamate repeat and the expression of proteins in the insulin-signalling pathway (that regulates life span) determine cellular toxicity of mutant huntingtin.(Morley ea, 2002) In animals, damage to mitochondria from 3-nitropropionic acid leads to a Huntington-like disorder; excitotoxic effects of NMDA may be an important additional factor in this model.(Perez-De la Cruz & Santamaria, 2007)

The earlier the onset of HD in the offspring of an affected father the greater the enlargement of the trinucleotide repeat sequence (CAG trinucleotide expansion – longest in juvenile cases) in the abnormal gene. There is degeneration of cells in the caudate nucleus²⁸⁷⁰, putamen and cerebral cortex.



Head of caudate indenting ventricle (coronal section)

The number of neurones in the striatum are diminished, especially the small to medium-sized spiny neurones. The aspiny neurones are relatively spared. Changes in the dendrites of spiny neurones are more extensive in the caudate than in the putamen. Neuronal intranuclear inclusions containing huntingtin and ubiquitin develop in humans and transgenic mouse models of HD.(Maat-Schieman ea, 2007) GABA deficiency with a relative excess of dopamine has been confirmed. Enkephalin deficiency is also reported. The EEG shows changes only late in the course of HD. The clinical features depend to some extent on the age of onset: young adults – rigidity (*Westphal variant*), middle years – chorea, and old age - cerebellar signs. Features include personality problems, schizophrenia-like psychosis, depression²⁸⁷¹, suicide (3-20 times the rate of the population at large), chorea, facial grimacing, dysarthria, often an explosive speech, a shuffling or dancing gait, cessation of abnormal movements in sleep, weight loss despite a good appetite,

Hartnup's disease (inborn failure to absorb tryptophan and urinary tryptophan loss), isoniazid treatment (B6 deficiency), and phaeochromocytoma and carcinoid syndrome (tryptophan is used to form amines instead of nicotinamide in the latter two disorders).

²⁸⁶⁵ Backs of the hands and neck (Casal's necklace) but also skin around anus and vulva.

²⁸⁶⁶ HD was described by George Sumner Huntington (1851-1916) of Long Island in 1872, although John Elliotson of London (1791-1868) may have predated him.(Elliotson, 1832/3) It was previously known as 'the magrums'.

²⁸⁶⁷ Massive expansion of the triplet repeat can cause the disorder to manifest in infancy.(Seneca ea, 2004)

²⁸⁶⁸ The exact rate varies with different authors, from rare to 10%.

²⁸⁶⁹ Huntingtin is found in all human and mammalian cells, with highest concentrations in brain and testis. It appears to have excitotoxic potential.

²⁸⁷⁰ CT shows atrophy of the caudate head. Resultant dilatation of lateral ventricles gives a 'butterfly' appearance.

²⁸⁷¹ About 3 in 1,000 people diagnosed with major depression were reported to have CAG trinucleotide expansion.(Perlis ea, 2010)

and dementia. Authors differ in their findings of psychiatric problems among close relatives of Huntington patients, interpreting their results as indicating heredity or shared environment (or both) accordingly. The so-called 'milkmaids sign' is a method of exaggerating the chorea by grasping the examiner's fingers (and squeezing them) in the same way as one tests for power.²⁸⁷² The chorea may also be exaggerated by getting the patient to stretch out his hands in front of him. Memory disturbance is only moderate. Attention, problem-solving, and arithmetical skills are more prominently affected. (Goldstein ea, 2002) The patients is apathetic and distractible and judgement is often poor. The patient often remains aware of intellectual dysfunction. Common complaints are of being confused, slowed up, and difficulties with remembering. Language is preserved. Focal cortical deficits are absent. Treatment is symptomatic. Antipsychotic drugs and tetrabenazine may decrease chorea but should only be used if really necessary because of unwanted side-effects. Injection of foetal striatal cells into the caudate nucleus and putamen has led to improvement in some cases. However, numbers were small and follow up was short. Excessive activation of glutamate-gated ion channels kills neurones via oxidative stress and may have a role in the pathogenesis of HD (cf. above), and α -tocopherol²⁸⁷³ may have a protective role in reducing early motor decline. Coenzyme Q10, effective in transgenic mouse HD, is being tested. (Walker, 2007) The differential diagnosis is mainly from tardive dyskinesia and AD.

Frontotemporal dementias (FTD)²⁸⁷⁴

According to Snowden ea (2002) FTD may account for up to one fifth of cases of presenile dementia cases. Farrell (2007) gives the prevalence of FTD as 15/10,000, second after AD as a cause of *presenile* degenerative dementia. The frontal and temporal lobes are principally involved. There may be a positive family history in up to half of these cases. The microtubule-associated protein tau (MAPT) gene on chromosome 17q21 may have a role in some (but not all) familial cases of frontotemporal dementia²⁸⁷⁵. FTD can be divided into FTD-tau and FTD-U, clinically similar but pathologically different. In FTD-tau there is abnormal hyperphosphorylation of tau with widespread tau deposition in neurones; FTD-U shows widespread ubiquitin immunopositivity with lentiform neuronal nuclear inclusions. (Farrell, 2007) Null mutations²⁸⁷⁶ causing reduced transcription of progranulin²⁸⁷⁷ may be responsible for some cases of FTD. Defective serotonergic activity is commonly reported in FTD but the cholinergic system is spared. The EEG is classically normal in FTD and seizures are rare²⁸⁷⁸. HMPAO-SPECT may demonstrate diminished blood flow or metabolic activity in the anterior part of the brain despite relatively normal CT or MRI scans.

There are pronounced changes in affect and personal and social conduct: 'The salient clinical characteristic is a profound alteration in character and social conduct, occurring in the context of relative preservation of instrumental functions of perception, spatial skills, praxis and memory'. (Snowden ea, 2002)²⁸⁷⁹ The patient appears indifferent. Both FTD and AD are associated with executive dysfunction and confabulation, confabulation being more common in FTD. Loss of function in the left anterior temporal lobe in people with frontotemporal dementia may increase artistic and musical skills! Motor problems may appear long before dementia. Weight gain due to overeating gives way to weight loss due to apathy. Dysphagia is common. Dysautonomia may lead to hypotension, cold extremities and other problems. Death may be sudden either for unknown reasons or because of autonomic dysfunction or (due to hyperorality) choking. Young people may be diagnosed as having 'schizophrenia' or 'schizoaffective disorder' years before a diagnosis of FTD is made. (Velakoulis ea, 2009)

²⁸⁷² The patient's fingers move as if mimicking what one does when milking cattle.

²⁸⁷³ This (vitamin E) reduces oxyradical-induced membrane damage.

²⁸⁷⁴ Baldwin (1993) argued that there are a group of lobar or localised dementias that may be more common than is generally recognised and that are not due to other causes, such as AD, Pick's disease (others, such as Dermaut & Van Broeckhoven [2002] include Pick's disease among the frontotemporal dementias which makes epidemiological interpretation difficult), or CJD. Hodges (2001) states that there are 3 distinct types of FTD: frontal variant FTD, semantic dementia, and progressive non-fluent aphasia (primary progressive aphasia).

²⁸⁷⁵ The mutations alter binding of microtubules to tau or lead to production of one isoform of tau rather than another. There are 6 known tau isoforms.

²⁸⁷⁶ Stop mutations and intronic mutations in splice donor sites and in the initiation codon.

²⁸⁷⁷ The progranulin gene is 1.7 Mb from the tau gene. Progranulin is involved in development, repair, inflammation (it is increased in activated microglia in AD and a number of other neurodegenerative disorders), and tumour formation.

²⁸⁷⁸ qEEG may show differences between AD and FTD and some chromosome 17 mutations may lead to early seizures.

²⁸⁷⁹ If the picture is one of loss of executive functions and problems with speech and memory is minimally affected then it is likely that the frontal lobe is mainly affected.

*PEMA syndrome*Palilalia²⁸⁸⁰

Echolalia

Mutism (late)

Amimia²⁸⁸¹

Typical of FTD

Rare in AD

*Other associations with FTD*Amyotrophic lateral sclerosis (ALS)²⁸⁸²

Progressive supranuclear palsy

Parkinsonism (PD)²⁸⁸³Dementia due to fragile X-associated tremor/ataxia syndrome (FXTAS)²⁸⁸⁴Cortico-basal ganglionic degeneration²⁸⁸⁵

Pasquier ea (2003) suggest trying trazodone for behavioural disturbance. Cholinesterase inhibitors may worsen behaviour. There is a suggestion that FTD is associated with hypersensitivity to antipsychotic drugs. (Pasquier ea, 2008, p. 469)

Pick's disease²⁸⁸⁶

This uncommon disorder usually manifests around 50–60 years of age. It is characterised by bands of 60 and 64 kDa phosphorylated tau. Gray and Cummings (1999) suggest that Pick's disease accounts for about one-fifth of cases of frontal lobe dementias. An incompletely penetrant autosomal dominant inheritance has been suggested. Two women are affected for every man. A majority will die within 4 to 6 years. A Pick's brain may be as light as 1,000 gm. Atrophic changes occur chiefly in the frontal and temporal lobes²⁸⁸⁷. The gyri show a characteristic brownish 'knife blade (or knife edge) atrophy'²⁸⁸⁸. Gliosis occurs in the white matter under cortical grey matter. Cell loss occurs and other cells may be ballooned. Pick bodies are within neurones and can displace the nucleus. Symptoms vary but include personality change (emotional blunting, egocentricity, mild euphoria, and fleeting anger), aphasia, echolalia, palilalia, perseveration, mutism and incontinence. Memory loss is relatively late. Catastrophic reactions to failure are absent. Kluver-Bucy elements (hypersexuality, placidity, and hyperorality) are not uncommon. Patients can find their way about, dress, cook (although repetitiously) and sew (with reduced dexterity). Wasting is less marked than in AD. Many cases are diagnosed at postmortem examination although CT, MRI and brain biopsies have increased the numbers diagnosed during life. In a Minnesota autopsy series (Heston and Mastri, 1982) Pick's disease accounted for about 5% of cases regarded as progressive dementia in life, and AD accounted for about 70%. Differences in cholinergic markers and somatostatin, which distinguish AD, are not present in Pick's disease.

Reflecting the confusion surrounding nosology of the dementias, Foster (2003, p. 1050) states that Pick's disease is not hereditary and that previously reported cases of familial Pick's do not have Pick bodies and are due to a tau mutation, and should be classified as frontotemporal dementia with Parkinsonism linked to chromosome 17.

²⁸⁸⁰ Stereotypy of speech: repeating one's own words.

²⁸⁸¹ Inability to express oneself by using signs or gestures.

²⁸⁸² The FTD-ALS and FTD-PD were linked to the tau locus on chromosome 17. (see *Wilhelmsen- [Tim] Lynch syndrome* [of Dublin]: Lynch ea, 1994; Wilhelmsen ea, 1994)

²⁸⁸³ Rigidity is very common. Hemiparesis may occur with asymmetrical cases.

²⁸⁸⁴ **FXTAS:** Grandfathers of cases of fragile X syndrome have frontal, subcortical, and motor manifestations: executive dysfunction, psychomotor slowing, amnesia, tremor, ataxia, and rigidity. Cortical and cerebellar atrophy are generalised. There is increased signal intensity in the middle cerebellar peduncles on neuroimaging. The FMR1 gene (Xq27.3) is altered. This condition resembles Parkinson's disease plus dementia. Cognition and neurological status progressively deteriorate. (Jacquemont ea, 2003)

²⁸⁸⁵ Loss of neurones in basal ganglia and fronto-parietal cortex., with atrophy of latter on MRI. Intracellular accumulated tau protein.

²⁸⁸⁶ Described by Arnold Pick of Prague in 1892.

²⁸⁸⁷ Unlike parieto-temporal changes in AD.

²⁸⁸⁸ Ulegyria.

Progressive subcortical gliosis

Rare dementia described as 'Pick disease type II' by Neumann in 1949. Most cases start insidiously in their 40s or 50s. Age of onset is not affected whether cases are familial or sporadic and the sexes appear to be affected equally. Although it resembles Pick's it has a distinct neuropathology. Tau gene mutation has been reported. There is genetic linkage to 17q21-22. Progress: personality/emotional change; reduced judgement and insight; problematic social behaviour; delusions, paranoia, auditory/visual hallucinations, and depression - decline in memory and speech output and word-finding difficulties (some have verbal stereotypes, acholalia, or Klüver-Bucy syndrome) - late cases are densely demented, akinetic/mute, incontinent, dysphagic, and have extrapyramidal signs.

Primary progressive aphasia²⁸⁸⁹ (PPA)

PPA is the presenting picture in about one-tenth of dementias. There is often an initial word-finding difficulty (dysnomia) with relative (to AD) preservation of memory and non-verbal cognition. Typically, the case progresses from dysnomia to non-fluent aphasia with anomia. The disorder may progress extremely slowly. AD is often the end result. However, a severe form of motor neurone disease can also develop. An alternative end point is corticobasilar degeneration. Alien hand syndrome has been reported, although this has been disputed²⁸⁹⁰. Atrophy predominates in the left temporal lobe. SPECT reveals greatly reduced tracer uptake in left frontal, temporal and parietal areas.

Semantic dementia (temporal variant of FTD)

This is a very rare condition. As a result of bilateral atrophy of middle and inferior temporal gyri²⁸⁹¹, these patients have fluent speech with semantic errors and poor comprehension and naming²⁸⁹². There is associative agnosia with impaired identification of sounds, odours, place, objects, etc. The patient's interests narrow, often becoming extremely focused on one activity. There may be loss of awareness of danger. Interestingly, and unlike AD, older memories may be affected more than newer ones²⁸⁹³. SPECT shows reduced bilateral (often left more than right) tracer uptake in the temporal region.

Creutzfeldt-Jakob disease (CJD)

Creutzfeldt-Jakob²⁸⁹⁴ disease is a rare condition that ends fatally within two years, with most cases dying well before a year is past. (O'Shea, 2001a,b) Treatment is non-specific. The incidence of CJD is about 0.5 cases/ million of the population/ year, with a higher incidence in parts of Slovakia and in Libyan-born Israelis.²⁸⁹⁵ The latter high-risk groups might inherit the disorder rather than become infected through their diet. Contact between cases is most unlikely.

Transmissible spongiform encephalopathies (Puoti ea, 1999)

Heterogeneous group of animal and human conditions

Neurodegenerative

Cellular prion²⁸⁹⁶ protein converted into disease-specific species

These altered isoforms account for neuropathology and transmissibility

²⁸⁸⁹ Pure progressive aphemia, progressive aphasia sans dementia, progressive non-fluent aphasia. Described by Mesulam in 1982. (Mesulam, 2003)

²⁸⁹⁰ Simple grasping movements are undisputed.

²⁸⁹¹ Semantic dementia is associated with involvement of the **left** temporal lobe; dysfunction of the right temporal lobe is associated with prosopagnosia.

²⁸⁹² Patient may give a broad superordinate response, e.g. 'clothes' when shown a hat.

²⁸⁹³ This may be due to relative hippocampal sparing.

²⁸⁹⁴ This is sometimes written as Jacob. Hans-Gerhard Creutzfeldt and Alfons Jakob described this condition independently of one another.

²⁸⁹⁵ A total of 23 cases of CJD in all its forms were reported in *Ireland* during the period 1996-September 2002. Sporadic cases reached a high of 6 in 1998. There was one case only of variant CJD (vCJD), in 1999, and one case of iatrogenic CJD, in 2001. Included in the total is one case of fatal familial insomnia, reported in 1997. Between 1999 and 2004 there were a total of 19 cases of definite sporadic CJD (plus 6 possible cases), 2 cases of vCJD, and the one cases of iatrogenic CJD mentioned above. Incidence rates of all types of CJD varied during that period from 0.5 (1999) to 2.01 (2004) per million. The incidence of CJD in the *EU* in 1994 varied from 0.53/million person years (mpy) in Italy to 1.04/mpy in the Netherlands, with the UK figure being 0.93/mpy.

²⁸⁹⁶ Carleton Gajdusek (1923-2008) was awarded Nobel Prize in 1976 for discovering what he called a slow virus, now known as a prion.

There is no particular association between any occupation and CJD, including farming, and no proven association with the national incidence of BSE. However, the rarity of CJD and the long incubation period of 2 to 30 years or more may put the peak incidence of sporadic disease in the 70-79-year-old age group and so be easily missed. The mean age of onset is 65 years for the sporadic type and 29 years for the variant type, with mean duration of illness being 4 and 14 months respectively.

Prion²⁸⁹⁷ protein is a membrane glycoprotein present in most organs, including neurones. The human PrP gene²⁸⁹⁸ (PRNP) is a single-copy gene located on the short arm of chromosome 20²⁸⁹⁹. Prion proteins move cyclically from the cell membrane into the cytoplasm where they are digested by lysosomal enzymes. Pathological prion proteins also move into the cell but resist degradation, instead aggregating to form prions. Normal cellular prion protein is present chiefly in α -helical conformation. Pathological prion protein is mainly in a β -sheet conformation.

There are inherited²⁹⁰⁰, iatrogenic²⁹⁰¹, and sporadic²⁹⁰² forms.

Accumulation of this abnormal protein is central to the pathogenesis of the spongiform encephalopathies. Small virus-like particles were observed in hamster brains deliberately infected with scrapie and these can be isolated from CJD brains and identified electronmicroscopically. Histology of CJD shows astrocytosis, loss of neurones, and a spongiform²⁹⁰³ encephalopathy. Cortex, deep nuclei and cerebellum are involved. Amyloid plaques are seen in only 5% of cases. A role for apolipoprotein E has been suggested.

Related disorders: The 'subacute spongiform encephalopathies' are possibly caused by the same or related prions. In animals they cause scrapie²⁹⁰⁴, spongiform encephalopathy in cats, chronic wasting disease in elk and deer, transmissible encephalopathy in mink, bovine spongiform encephalopathy (BSE), and many others. In man they cause kuru²⁹⁰⁵, Gerstmann-Straussler-Scheinker²⁹⁰⁶ syndrome (GSS) and CJD. In all of these conditions one can find fine meshed vacuolation, astrocytic proliferation, fibrillary gliosis, delayed loss of neurones, minimal demyelination, and a propensity to attack the cerebral cortex, basal ganglia and cerebellum. Amyloid plaques are also found. The scrapie agent is sub-microscopic. GSS has a more insidious course than CJD; there is less vacuolation and many amyloid plaques.

Virology: CJD agent, a 'slow virus'²⁹⁰⁷, contains only protein, i.e. a prion. One theory is that the host's cell already contains the DNA sequence necessary to produce a peptide that in turn infects the host. Prions are thought to be about the same size as viroids²⁹⁰⁸.

Transmission: Spongiform encephalopathies can be experimentally transmitted to a range of species not showing a natural tendency to develop these conditions. BSE (mad cow disease) sets cattle wild, mad and falling. BSE is thought to be due to feeding cattle with meat and bonemeal derived from sheep offal, with transmission of the scrapie agent. (Alternative theories include transmission of human prion to cattle that were then imported from India, origin other species, iatrogenic, PRNP gene mutation²⁹⁰⁹, various host factors, organophosphate pesticide exposure, high manganese or low copper levels in soil, and *Acinetobacter* bacteria in cattle feed: Colchester & Colchester, 2005.) This practice has been outlawed. It

²⁸⁹⁷ 'Subvirus' or proteinaceous infectious agent (term coined by Stanley Ben Prusiner of California, b. 1942, neurologist and biochemist, Nobel Prize in Medicine 1997) – contains no genetic material. The abbreviations employed in the literature for various forms of prion protein are at least confusing: PrP^c for normal prion protein; PrP^{sc} for all pathological forms of the protein, sc standing for scrapie; Δ PrP for inherited cases; and PrP^{sp} for sporadic cases.

²⁸⁹⁸ Protease-resistant prion protein.

²⁸⁹⁹ PrP means protease-resistant prion protein.

²⁹⁰⁰ Due to one of many mutations in the PRNP gene: 5-15% of cases.

²⁹⁰¹ See later – foreign prion protein might act as a template that causes conformational change in normal prion protein from α -helix to β -sheet: rarest form.

²⁹⁰² ? age-related spontaneous mutation or some earlier environmental event: 85% of cases.

²⁹⁰³ Vacuolation of neurophil. The vacuoles consist of swollen axons and dendrites.

²⁹⁰⁴ Affecting sheep and goats; sheep 'scrapes' its wool against wooden fences.

²⁹⁰⁵ 'Trembling disease' of Fore Tribe, New Guinea. Kuru plaques have surrounding spikes.

²⁹⁰⁶ **Gerstmann-Straussler-Scheinker syndrome:** Rare (1-10/million population) familial disorder affecting those with a specific autosomal dominant defect in chromosome 20, i.e. mutations in PRNP gene. It usually presents in fourth/fifth decade with progressive ataxia, dysarthria, extrapyramidal signs, and dementia and lasts about 7 years. Pathologically it looks like a combination of AD (except that plaques mainly contain PrP) and spongiform changes with gliosis.

²⁹⁰⁷ A very long incubation period and a profound resistance to inactivating agents. In fact, prions are not viruses.

²⁹⁰⁸ Smallest life form: naked RNA with no protein coat; cause plant diseases.

²⁹⁰⁹ PRNP polymorphisms may act as susceptibility or protective factors for human prion diseases such as CJD and kuru. (Mead et al, 2009)

has been postulated that mink may become affected in the same way. Domestic cats have been infected with BSE from eating cat food that use cattle offal.

CJD transmission may occur via injected brain tissue²⁹¹⁰, infected in-dwelling cerebral electrodes, pituitary extracts, (cadaveric) human growth hormone²⁹¹¹, and corneal or tympanic transplants, and, possibly, wild animals. Up to 15% of cases have a family history of the condition and a dominant inheritance pattern. It is possible that an uncommon prion genotype confers susceptibility to infection with exogenous prion, although the nature of the prion protein-gene interaction is unknown.

Kuru may have been spread by cuts and by mucous membranes during ritual ceremonies with affected corpses²⁹¹². Prion diseases can be familial or sporadic. Familial spongiform encephalopathy is associated with mutations in the normal (harmless) prion protein (PrPc) gene, the latter coding for a normal cell surface protein²⁹¹³. This protein accumulates in CJD and GSS and is deposited in plaques as amyloid (prion amyloid is different to Alzheimer amyloid). In prion disease it is this protein that becomes resistant, as PrPsc (scrapie prion protein), to proteolysis and is itself infectious.

Fatal familial insomnia (FFI) is a rare, untreatable prion-induced spongiform encephalopathy²⁹¹⁴ characterised by progressive insomnia, dysautonomia, and motor signs. Chronic hypertension without the expected fall in blood pressure during sleep, elevated cortisol and catecholamine levels, and disturbed rhythms of melatonin, prolactin, and somatotrophin may be found. FFI is a PRNP mutation disorder (chromosome 20): **D178N mutation** causes the disorder when codon 129 codes for **methionine**. When the same codon codes for **valine** the result is CJD. Patients usually die within a year. The thalamic nuclei undergo atrophy. Protease-resistant PrP can be demonstrated, albeit weakly, by immunoblotting.

Clinical features: CJD typically comes on during the sixth or seventh decades with memory loss, or, less commonly with changes in behaviour or higher cortical deficits such as dysphasia or dyslexia. Over several weeks there follow frank dementia, visual (cortical blindness) or co-ordination problems, rigidity and involuntary movements, particularly myoclonic jerks, the latter often occurring in synchrony with periodic electroencephalogram (EEG) periodic sharp and slow wave complexes (on a low voltage background). Signs of pyramidal and cerebellar damage may be elicited. Death usually occurs within 6 months.

Knight (1989) described three types of clinical picture in CJD: subacute lasting less than 6 months²⁹¹⁵; chronic form²⁹¹⁶; and an amyotrophic type.²⁹¹⁷

Phlebotomists should wear gloves when taking blood from demented patients as a precautionary measure. All suspected live cases should be reported to the Department of Neurology at St Vincent's Hospital, Elm Park, and all deceased suspected cases must have a post mortem examination at Beaumont Hospital.

Clinical diagnosis of CJD is usually reliable and accurate in the presence of dementia, myoclonus and periodic triphasic EEG discharges at 1-2 Hz, and the absence of both the latter two parts of the triad count against a diagnosis of sporadic CJD. However, the same EEG changes are found in hepatic encephalopathy, lithium intoxication, uraemia, and some rarer disorders (e.g. SSPE). Also, these triphasic EEG discharges are probably (sources differ) not found in vCJD.²⁹¹⁸ Lithium intoxication also causes myoclonus, but this and the EEG changes are reversible. Otto et al reported raised serum S100, a brain specific protein mainly found in glia that may be a marker for activated astroglia, in CJD. These levels were higher than those found in other diseases and showed 77.8% sensitivity and 81.1% specificity for CJD. S100 levels rise in serum after head trauma but decline quickly due to renal elimination. (Otto et al, 1998) PrP immunohistochemistry, using appropriate pre-treatments, will be positive in the great majority of cases.

²⁹¹⁰ E.g. human brain biopsy homogenate put into monkey brains.

²⁹¹¹ Used in USA for dwarfism from 1959 to 1985. Recombinant HGH used now instead.

²⁹¹² Cannibalism began in 1910, followed some time later by the earliest cases of kuru. (MacCormack, 2004)

²⁹¹³ **PrPc prion protein**, which contains many alpha-helices, is plentiful in nerve cells and seems to have a number of functions (neuroprotective, copper metabolism, and oxidative balance). PrPc may change to PrPsc, a beta-pleated peptide like the Aβ of AD, tends to form insoluble aggregates. Beta-pleated PrPsc is almost protease resistant and *can promote further PrPsc formation from PrPc*. It may be that when prion protein moves from the endoplasmic reticulum to cell membrane or cytosol that it is capable of damaging nerve cells. (Aguzzi & Polymenidou, 2004)

²⁹¹⁴ Mild spongiform changes in some cases.

²⁹¹⁵ Especially dementia, mutism, akinesia, hypertonia, myoclonus, normal CT scan, increased protein in cerebrospinal fluid (CSF) or a normal CSF, and periodic discharges in the EEG - non-specific slowing goes on to generalised periodic biphasic or triphasic complexes.

²⁹¹⁶ 8% of cases, usually lasts more than 2 years, similar to subacute form but lasts longer.

²⁹¹⁷ 5% of cases, usually lasts a few years, similar to a combination of motor neurone disease and dementia.

²⁹¹⁸ Triphasic waves are found (eventually) in most sporadic cases, in some inherited and iatrogenic cases.

Protease-resistant PrP, found in all known prion diseases, can be shown by immunoblotting of brain homogenates. Plasminogen binds to the pathological prion protein whilst ignoring its normal counterpart. The currently recommended approach to diagnosing sporadic CJD in the laboratory is to look for the 14-3-3 protein in the CSF by Western blot immunodetection.(Will ea, 2000) This is found in a majority of cases. It may also be present in vCJD and in about 10% of cases of MS (Martinez-Yelamos ea, 2001) and a few cases of fatal familial insomnia but is not found in Gerstmann-Straussler-Scheinker syndrome. False positives can occur with recent CVA, herpes simplex encephalitis, and paraneoplastic cerebellar degeneration and limbic encephalitis.

MRI may show 'cortical ribboning' on diffusion-weighted imaging.(Poser ea, 1999)

*Variant CJD*²⁹¹⁹ (vCJD): Will ea (1996) reported a variant syndrome in young British adults and adolescents that many have speculated might be due to eating beef.

vCJD

Starts with psychiatric and sensory symptoms
Neurological deficits, such as dementia and ataxia, are delayed
EEG is atypical
Patient exhibits anxiety, depression, behavioural problems, ataxia and dementia

The incidence of vCJD is higher in the north than in the south of Britain,(Cousens ea, 2001) with the largest cluster being in part of Leicestershire.(Dobson, 2001) The latter phenomenon may relate to a n outdated butchery practice that allowed infected brain tissue contact with meat.

First 14 cases of vCJD in UK (Zeidler ea, 1997a)

10 examined when alive
8 of 14 were female
Mean onset at 29 years (range: 16-48)
Median duration of 14 months (range: 9-35)
Early psychiatric symptoms in all, especially depression
8 had early, persistent, often painful sensory symptoms
All had neurological signs, including ataxia and involuntary movements e.g. chorea and myoclonus
Most had terminal akinetic mutism
EEG mostly abnormal but absence of CJD periodic complexes
CT normal or non-specifically abnormal
2 cases had high thalamic MRI signal
Diagnosis was neuropathological

Psychiatric symptoms in vCJD (Zeidler ea, 1997b)

Common and include:
Depression (main diagnosis)
First rank symptoms (minority)
Transient delusions
Auditory or visual hallucinations

Large aggregates of prion protein are seen in cerebellum and basal ganglia. The hallmark on brain biopsy is the presence of dense eosinophilic amyloid plaques, staining positive with anti-PrP antibody, with a pale periphery surrounded by a zone of spongiform change. These are similar to lesions found in animal brain after intracerebral inoculation with BSE cattle brain homogenate. When vCJD was transmitted to mice they

²⁹¹⁹ **Will-Ironside syndrome** or **(new) variant CJD**. Brown (2001) goes further and insists that BSE is the cause of vCJD, that scrapie from sheep caused BSE in bovines by crossing the species barrier, and that changes in rendering of livestock carcasses allowed infectivity to survive and contaminate meat and bone meal in livestock feed, amplifying infection to epidemic proportions. The same author holds that the export of contaminated meat and bone meal and live cattle incubating BSE spread the disease outside Britain; and that BSE caused vCJD through adulteration of cooked meat products with mechanically recovered meat contaminated by compressed spinal cord and paraspinal ganglia.

showed BSE-like change. vCJD may be diagnosed by tonsil biopsy²⁹²⁰ but brain biopsy remains mandatory in order to outrule treatable disorders like vasculitis or Whipple's disease. Zeidler ea (2000) reported bilateral increased pulvinar (posterior thalamus) signal on T2-weighted MRI – the 'pulvinar sign'²⁹²¹ to have 78% sensitivity and 100% specificity for vCJD. The specificity of the 'pulvinar sign' is not as strong as this report suggests, although it is a welcome addition to invasive tonsil biopsy. FLAIR sequences may reveal the 'hockey-stick sign' (hyperintense pulvinar and dorsomedial thalamic nuclei). (Zeidler ea, 2000) Other findings included medial thalamic and periaqueductal grey matter high signal, and a notable absence of cerebral atrophy.

As far as host susceptibility to vCJD is concerned, all cases have the same normal allelic variant (MM) at codon 129 of the gene for cellular prion protein, (Will ea, 2000) i.e. all patients with vCJD reported so far (and most cases with sporadic CJD) are homozygous for amino acid methionine at position 129, whilst heterozygosity at this position appears protective.²⁹²² Because 38% of the UK population carry the high risk amino acid methionine 129 and since so few people seem to develop cCJD, other factors must be involved, e.g. a lower incidence of HLA DQ7 was thought to confer susceptibility but replication studies failed to confirm this. HLA molecules present antigenic peptides to the immune system.

The current method of diagnosis of vCJD rests on tonsil biopsy. Zanusso ea (2003) have found PrP^{sc} in olfactory cilia and the central olfactory pathway, but not in respiratory mucosa, in deceased cases of sporadic CJD, which may offer a new route for biopsy. The future may see the availability of a test using erythroid-differentiation-related factor (EDRF) which starts to fall early in the disease and falls further with disease progression. EDRF and prion protein co-localise and EDRF transcripts are easily measured in blood by northern blotting. Selective affinity resins are being developed to remove endogenous transmissible spongiform encephalopathies present in blood. (Gregori ea, 2006; Turner, 2006)

In conclusion, CJD has rapidly changed from being seen as a rare, esoteric disorder to occupying centre stage in medical thinking. This elevation was caused by the BSE crisis initially and later by reports of both iatrogenic and variant forms of the disease.

Aspects of CJD

Hans-Gerhard Creutzfeldt (1885-1964) and Alfons Maria Jakob (1884-1931) described the condition in 1920 and 1921 respectively, the latter naming it 'spastic pseudosclerosis'.

1950s: extraction of hormones from cadaveric pituitary glands

1985: UK, US, and other countries halt distribution of growth hormone after 3 deaths.

1986: first cases of BSE.

1970s: CJD transmitted via corneal transplants, depth electrodes, and neurosurgical instruments.

1990: Feline spongiform encephalopathy cases in UK; ban on specified animal offal in pet food.

UK deaths secondary to use of cadaveric pituitary gland [growth hormone (GH) or gonadotrophins] (by then replaced by genetically engineered growth hormone).

1993: Kuru cases reported despite abandonment of cannibalism in 1950s.

Illegal surgical use of cadaveric materials in some countries is a potential source of CJD; athletes using human growth hormone may be at risk.

1995: vCJD in UK.

1997: CJD transmission of via cadaveric dura mater grafts.

1997: controversial, preliminary evidence concerning CJD transmission via blood and blood products.

1998: 6 young adults treated with human GH receive compensation for distress of being at risk of CJD.

Suggestion that vCJD is due to changes in rendering process of sheep carcasses, causing scrapie in cattle, or to a novel strain of scrapie or BSE resistant to rendering?

1999: first case of vCJD in Republic of Ireland.

ROI: CJD a notifiable disease: Irish National CJD Surveillance Centre resides at St Vincent's (clinical – 01-8092643) and Beaumont (neuropathology – 01-2094412) Hospitals, Dublin²⁹²³.

2000: BSE transmission to rodents and sheep by blood; small number of UK children develop vCJD.

2001: UK government to use disposable tonsillectomy equipment, Ireland may follow.

2001: A case of iatrogenic CJD notified in Ireland.

2002: Male dies of vCJD in Canada; probably contracted in Britain.

2002 (May): 128 cases of vCJD in UK, France and Ireland.

2002: vCJD case diagnosed in Italy (see October *Lancet*).

²⁹²⁰ By demonstrating characteristic PrP immunostaining and PrP^{sc} on western blot. Tonsil biopsy allows early and pre-symptomatic diagnosis. (Wroe ea, 2006)

²⁹²¹ 'Pulvinar sign' – this is also found in, e.g., paraneoplastic limbic encephalitis and Wernicke-Korsakoff syndrome. This sign - bilateral thalamic hyperintensity in T2 proton-weighted images – is due to gliosis.

²⁹²² See Partenen (2003) for review.

²⁹²³ UK Surveillance Unit is based in Edinburgh, Scotland.

2003: Swiss scientists find abnormal prions in spleen and skeletal muscle in sporadic CJD.

2003: UK patient dies of vCJD who may have acquired it from a blood transfusion: the donor gave the blood in 1996 and died of vCJD in 1999.

2003: Ireland reported to have an incidence of 0.75 cases of CJD/million/year, not dissimilar to neighbouring European countries. 26 cases of CJD (incl. vCJD) were recorded in Ireland 1996-2003.

2005: BSE reported in a goat in France in January.

2006: Irish coroner remarks on two fatal and one living cases of vCJD with addresses within 5 miles of one another.

2006: First Japanese case of vCJD in 50 year old man who was in UK in 1990 and showed mental symptoms from 2001, akinetic mutism in 2003, and died of pneumonia in 2004.

2006: Findings from appendix (homozygous **valine** genotype in tissue that harboured prion proteins) raises the spectre that ongoing iatrogenic transmission may sustain the spread of vCJD.

2006: Eleven cases of kuru identified from July 1996-June 2004, all in South Fore and born before cannibalism ceased.

2008: Seven doctors and pharmacists on trial in France over death of at least 110 people who developed CJD after being given tainted human growth hormone in childhood²⁹²⁴.

(Idiopathic) Parkinson's disease²⁹²⁵

Lifetime risk for Parkinson's disease is around 1 in 50, increasing in the presence of affected relatives. DA-containing cell bodies in the *pars compacta* of the substantia nigra undergo degeneration. Hyaline material (Lewy bodies) is present in nigral cells. There is a reduction in neurone numbers in the locus coeruleus with loss of cortical noradrenaline occurring secondarily. Parkinson's disease with dementia is associated with greater atrophy of the hippocampus than is the case with Parkinson's disease without dementia; there is also less cortical atrophy than that found in AD; and there is cell loss in the nucleus basalis of Meynert. There is less cortical acetylcholine loss than in AD. Loss of raphe cells leads to 5-HT depletion, possibly explaining the excess of depression²⁹²⁶ and anxiety in these cases. Hentschel and Förstl (2008, p. 185) see Parkinson's disease and AD as extremes of a pathological spectrum with the Lewy body variant of AD occupying an intermediate position.

Parkinson's disease

↓ DA output from substantia nigra to globus pallidus – ↓ inhibitory action on subthalamic nucleus (STN) -
 ↑ activity of STN - ↑ cortical inhibition - bradykinesia²⁹²⁷

Cognitive impairment has been reported in from 20-40% (8-80%) of cases but most sufferers probably have some level cognitive impairment (bradyphrenia, impaired visuospatial ability, poor attention shifting, and executive problems). It may be that sufficient longevity will always be associated with dementia. (Aarsland et al, 2003) Dementia may be caused by a co-existing disorder, most often, AD²⁹²⁸, or by Lewy body degeneration in the nucleus basalis and cerebral cortex. Demented cases and non-demented cases show marked and modest cortical choline acetyltransferase deficiency respectively.

40% of cases are said to suffer from depression, although not all studies an excess of major depression over that found in age- and sex-matched physically disabled persons. There is a large element of anxiety and relatively little self-blame. Depression is more likely with reduced CSF 5-HIAA, a history of depression, or significant functional disability. Depression in Parkinson's disease may be due to involvement of frontal dopaminergic projections. PET studies suggest that reduced cerebral blood flow in the medial prefrontal cortex may be common to primary depression and depression in Parkinson's disease. The depression responds to antidepressant drugs²⁹²⁹ and ECT. ECT may also improve physical function in Parkinson's disease. Indeed, some patients benefit from maintenance ECT. (e.g. Shulman, 2003) Neuroleptics can

²⁹²⁴ Some donor cadavers had neurological, dementing, or infectious disorders and gland were pooled. (King, 2008)

²⁹²⁵ This was described by James Parkinson of Hoxton in London in 1817. Parkinson described a patient who made his servant walk ahead of him so that he could be stopped when his slow gait would suddenly accelerate! Famous patients with this disorder include Pope John Paul II, Kenneth Moore, Muhammad Ali, Michael J Fox, Dame Anna Neagle, Janet Reno, and AJP Taylor.

²⁹²⁶ As with clinical Parkinson's disease, depression is a frequent problem in community-dwelling elders with parkinsonism, even in the absence of functional disability. (Braam et al, 2009)

²⁹²⁷ Anticholinergic drugs reduce tremor and rigidity but do not reduce bradykinesia.

Freezing: The bradykinetic or akinetic patient may freeze on intentionally trying to move. Such patients may use 'sensory tricks' (e.g. listening to stirring music or stepping over a crack) to overcome this. Freezing should not be mistaken as being 'psychogenic'.

²⁹²⁸ If the dementing patient develops early cortical symptoms (e.g. dysphasia) co-existing AD is suggested.

²⁹²⁹ TCAs can cause significant side effects, and nortriptyline may be the first choice; SSRIs can cause EPS and, if combined with selegiline [L-deprenyl], a serotonin syndrome. Dietary precautions are required for higher (9 or more mg) but not lower (6 mg) doses of selegiline, a selective, irreversible MAO-B inhibitor.

unmask latent Parkinson's disease. Amoxapine should be avoided in depressed Parkinson's disease patients because of its DA blocking actions.

Akathisia may precede use of medication in patients with Parkinson's disease.

Visual hallucinations may occur in Parkinson's disease patients even before they receive any medication.

Patients may have insight into the nature of these experiences at first but most will eventually react to them as if they were true perceptions when the disease becomes more established. Opinion about their pathogenesis is divided between dopamine dysfunction within the visual system and disrupted circuitry subserving regulation of REM sleep. (Wilson & Nutt, 2008, p. 88) All drugs used to treat this disorder can cause (especially at night) visual hallucinations and worsen cognitive function. Greater Lewy body load and cell loss in the amygdala increases the likelihood of developing hallucinations on exposure to levodopa. (Harding et al., 2002)

There are a few reports of mania²⁹³⁰, most likely due to medications such as levodopa. Most patients tolerate levodopa for years without developing psychosis. Psychosis in Parkinson's disease²⁹³¹ should be managed by reviewing any possible aetiological role of medication and failing any success there one might try low dose quetiapine, sulpiride or risperidone²⁹³². Low dose clozapine has been shown to work. A BZD is often all that is necessary for brief psychotic episodes²⁹³³. Nortriptyline or clonazepam may be used for panic attacks.

Pathological gambling may be induced by dopamine agonist therapy. (Wong & Steiger, 2007) Hypersexual behaviour and compulsive shopping may also occur in such circumstances. Treatment-induced stereotypies ('punding'²⁹³⁴) may take up much of the patient's time, e.g. purposeless putting together and taking apart of machines.

Reduced striatal uptake of dopamine in 'sporadic' Parkinson's disease patients *and* their asymptomatic co-twins has been demonstrated with PET. (Piccini et al., 1999) Mutations of genes encoding for alpha-synuclein and parkin have been identified in familial cases. In fact, a number of genes (PARK-1, PARK-2, etc) have been reported to be associated with Parkinson's disease but they collectively account for only a small proportion of cases. Parkinson's disease may be associated with mutations in the gene encoding glucocerebrosidase²⁹³⁵. (Sidransky et al., 2009) The pesticide rotenone causes a Parkinsonian syndrome in rodents. MPTP (methyl-phenyl-tetrahydropyridine), which resembles paraquat, caused severe Parkinsonism in drug abusers. Familial fatal Parkinsonism is a rare condition, therapeutically unresponsive condition, presenting in the fifth decade with severe depression and with death from respiratory failure 4-6 years later. Fahr's disease²⁹³⁶ (familial idiopathic calcification of the basal ganglia) is an uncommon disorder with progressive dementia, convulsions, and rigidity and sometimes a schizophrenia-like illness and Parkinsonism; cases may be sporadic or autosomal dominant and in one family linkage was found to a locus on chromosome 14.

Thioridazine was a favourite neuroleptic in Parkinson's disease when one was required, but this neuroleptic has become unpopular because of associated QTc concerns. Clozapine and quetiapine are preferred today.

Never combine MAOIs with L-DOPA.

Glabella tap test (Myerson's sign): The examiner taps the glabella just above the nasal root from behind the patient and counts the number of blinks. More than 3 blinks are the usual criterion for 'abnormality'. The sign is more often positive in Parkinson's disease than in drug-induced Parkinsonism. However it (> 3 blinks) can also be found in very anxious people and as a release phenomenon (primitive reflex) in association with dementia.

Surgery for Parkinson's disease may involve pallidotomy, thalamotomy, and thalamic stimulation. Lesions in ventral intermediate thalamic nucleus mainly relieves tremor. If the tremor is bilateral then thalamotomy

²⁹³⁰ A few patients increase the dose of their medication in order to induce euphoria.

²⁹³¹ Psychosis affects 7-14% of non-demented cases. Those with hallucinations tend to retain insight as in Charles Bonnet syndrome. (Carson et al., 2007, p. 343)

²⁹³² Doses in the range 0.75-1.5 mg/day risperidone were been recommended for dementia cases (Jeste et al. 2000) but there appears to be an increased risk of strokes.

²⁹³³ High-dose diazepam has been associated with Parkinsonism. (Kellert & Chadwick, 2004, p. 326)

²⁹³⁴ Punding was originally applied to the stereotypies found in association with chronic amphetamine abuse.

²⁹³⁵ Glucocerebrosidase deficiency causes Gaucher's disease. Sufferers from the latter disorder can develop Parkinsonism and their relatives (who may be heterozygotes) have an increased risk for Parkinson's disease.

²⁹³⁶ Fahr disease is not the same as Fahr syndrome. The latter refers to basal ganglia calcification secondary to hormonal (e.g. hypoparathyroidism) or metabolic disorders (e.g. disorders of phosphate-calcium metabolism).

must be bilateral. Bilateral thalamotomy may interfere with gait and speech. Pallidotomy reduces tremor, rigidity, and bradykinesia contralaterally. It also is effective for medication-related dyskinesia. Bilateral pallidotomy may cause speech and cognitive problems. Brain stimulation, usually bilateral for better results, may also lead to slurring of speech. However, thalamic stimulation may occasionally yield dramatic improvements. Autologous adrenal medullary tissue transplantation has given less than hoped for results and may be complicated in the post-surgical period by psychosis, confusion and affective change. Fetal dopaminergic cell transplantation has excited ethical debate.

Acquired Immune Deficiency Syndrome (AIDS)

Of 33 million people living with HIV/AIDS worldwide in 2008²⁹³⁷, 67% live in Africa. Two million people succumbed to AIDS in 2007 and 24 million died from the disease during 1980-2007.(Bongaarts ea, 2010) HIV is involved in a titanic struggle in the body²⁹³⁸, eventually exhausting the immune system. CD4 T-helper lymphocytes are the preferred target of the HIV virus, the virus using the CD4 molecule as receptor²⁹³⁹. Viral reverse transcriptase is the intracellular catalyst for the conversion of viral RNA to DNA, the latter becoming incorporated into host chromosomes. Cellular activation leads to copying of this DNA leading on, with the assistance of protease, to HIV particles. HIV invades the CNS early on in the course of infection, entering via macrophages. These and microglia are mainly responsible for replication of HIV in the CNS. *HIV does enter CNS neurones*. It possibly causes neuronal damage via microglial neurotoxin production. It has been suggested that quinolinic acid, possibly derived from HIV-infected monocytes and a selective activator of NMDA receptors, may play a role in the development of AIDS dementia.(Duka, 2002)

The breakdown by type of case is shown in the table.²⁹⁴⁰ HIV/AIDS is not a notifiable disease in Ireland. There is not one laboratory responsible for collating confirmed results and the practice of using initials

²⁹³⁷ The figure for 1988 was 5 million.

²⁹³⁸ A mutation in the gene for the **Duffy antigen receptor chemokines** (DARC) occurs only in people of African descent. It prevents expression of DARC on red blood cells thereby eliminating the site where *Plasmodium vivax* attaches to the cell (useful in malarial areas) but it increases the risk of HIV infection by about 40%. **Male circumcision** has been said to reduce the risk of acquiring HIV (Siegfried ea, 2009) through vaginal intercourse (at least from women to men), although not all research agrees (Wawer ea, 2009) - the foreskin's (the latter acting to retain HIV-containing secretions) Langerhans cells are particularly vulnerable to HIV infection.(Roehr, 2007; Bailey ea, 2007; Gray ea, 2007; Katz & Wright, 2008) Unhygienic circumcision may increase risk of HIV in Africa (Moszynski, 2007) and surgical procedures are not popular.(Katz & Wright, 2008) It seems that **condom** use is still necessary after male circumcision if HIV spread is to be controlled.(Wawer ea, 2009)

²⁹³⁹ CD4 receptors are common in brain tissue. 80% of circulating lymphocytes are T cells (expressing CD antigens 1-5, 7 and 8) which mediate cellular immunity. The two main types are CD4+ helper cells and CD8+ suppressor cells.

HIV contains 2 molecules of single-stranded RNA. Reverse transcriptase polymerase converts viral RNA into DNA. Protease is also present in the virus. The core protein (p24, surrounding the 'nucleus') level can be employed in monitoring the disease. Outside this is the matrix protein (p17). The outer envelope glycoprotein (p120) binds to molecules on the surface of CD4 cells - this interaction, together with the chemokine co-receptors CCR5 and CXCR4, is responsible for the entry of virus into the host cell. A transmembrane protein (gp41) is important for infectivity and cell fusion.

²⁹⁴⁰ Up to December 1993 there were 355,936 cases of AIDS in the USA and the American public health service spent more on AIDS research in 1992/3 than on heart disease.(Tanne, 1993) By the end of 1999 there were 113,167 cases of HIV, 299,944 cases of AIDS, and 430,441 cumulative deaths from AIDS in the USA.(Centers for Disease Control and Prevention, 1999) An estimated total of 42 million persons worldwide lived with HIV/AIDS up to the end of 2002 (e.g. 570,000 in Western Europe, 1.2 million in Eastern Europe/Central Asia, and 980,000 in North America) with the greatest concentration in Sub-Saharan Africa (29.4 million). As of December 2003, over a million people in the US were infected with HIV. The largest affected group were Blacks at 47% of the total. 45% of cases were MSM, followed by injecting drug users.(Roehr, 2005)

Of 941 HIV+ cases reported in Edinburgh up to September 1992, 55% were associated with injecting drug misuse. The number of HIV cases in the UK was 41,700 in 2001 and 49,5000 in 2002, an increased proportion deriving the infection abroad; gay and bisexual men accounted for 80% of the new HIV cases in 2002 that were likely to have been acquired abroad; there was a parallel increase in gonorrhoea and syphilis in gay people; there was also an increase in HIV in the heterosexual population (147 in 1998 and 275 in 2002 were most likely acquired in the UK).(Reviewing the Focus: HIV and Other Sexually Transmitted Infections in the United Kingdom in 2002) Mathers ea (2008) estimated that almost 16 million worldwide inject drugs and that 3 million of these might be HIV positive. 124 cases of AIDS were reported in Ireland between 1982 and 1989, rising from 2 during the first year to 50 during the last year. The number of cases had risen to 207 by July 1991 (with 1,101 HIV-positive cases and 85 deaths). The rate of infection was noted to be rising most rapidly among heterosexuals in 1992. By the end of June 1998 there had been 647 cases of AIDS (> 40% in IV drug users, about a third of cases were homosexual/bisexual, and 12.5% were heterosexuals), almost 2,000 HIV-positive cases and 328 deaths. During the whole of 1998 and 1999 there were 136 and 151 HIV-positive cases and 3 and 41 new AIDS cases and 4 and 17 deaths respectively, the total number of AIDS cases reaching 691 by the end of 1999. Over 80% of those deaths in 1999 were in males and most deaths were in the 25-35 year age bracket. According to an annual Durex survey (Anonymous, 2000b) two-thirds of 17-20 year old in Ireland have had unprotected sex.

rather than names of patients on specimens may lead to confusion in totals of cases. The majority of affected children now survive into adulthood.(Hermoine Lyall, 2002)

HIV/AIDS statistics for Republic of Ireland (RoI)

Note: figures and classification vary with source.

(a) Numbers of patients with AIDS in the RoI up to 2005*

	Total to end 1991**	Up to 30/6/94 cases (deaths#)	1999 (‘HIV’)	2001*** (‘HIV’)	2004^ (‘HIV’)	2005 (‘HIV’)
Heterosexuals	24	45 (21)	59	82 (59.4%)	178	159
<u>Men having sex with men (MSM)</u>				32 (23.2%)		
<u>Homosexuals/bisexuals (H/B)</u>	94	136 (67)	40		62	
H/B plus IV drug abuse	7	8 (06)				
IV drug abusers	100	177 (86)	69	11 (8.0%)		
Haemophiliacs	20	28 (20)				
Transfusion recipient				1 (0.7%)		
Mothers-to-child					3	
Babies born to IV drug abusers	8	8 (06)				
Undetermined	5	5 (03)				
Mothers	?	1 (00)				
Children			23	5 (3.6%)		
Prisoners			13			
Undetermined				7 (5.1%)		

*Undoubtedly there is cross-infection between the classes of patients listed here, e.g. IV users to heterosexual partners. The first needlestick-related case in Ireland was reported in 1995. The first case of HIV from needlestick in Britain’s NHS was reported in 1984, and a small number of deaths have since occurred.(Anonymous, 2003c)

**Kelly, 1994. #51% mortality rate.

***Last half of 2001 only (Source: National Disease Surveillance Centre). This gives a total of 138 newly diagnosed HIV cases for the third and fourth quarters of 2001. However, elsewhere the same group gives a figure of 299 new cases, down 9 cases on the year 2000! 75% of new HIV cases in 2001 were 20-40 years of age. Two of the children were born to HIV mothers and the transfusion recipient received the transfusion abroad.

Up to 31/3/97 the number of HIV+ cases came to 1,753, the number of AIDS cases totalled 593, and 308 deaths were recorded.

^356 HIV positive cases in 2004, a decrease of 57 from 2003. There were 41 AIDS cases in 2004 (fell from about 75 in 1994 to a low about 11 in 2000, and rising thereafter to over 40 in 2004).(Source: CSO health statistics).

(b) HIV cases in RoI 2006 onwards*

2006 – 337 reported new diagnoses (RNDs)

2007 – 362²⁹⁴¹ RNDs**

2008 (first half) – 170 RNDs***; (all year) 405 RNDs****

*Cumulative total of reported HIV cases to end 2007 was 4,781

**Health Protection Surveillance Centre got no reports from 30% of clinicians dealing with newly diagnosed cases! 146, 75 and 54 of 362 cases were heterosexual contacts, homosexual contacts and drug-related respectively.

***Total number of HIV infected cases to 30.6.08 = 4,951. Probable route of transmission known for 127/170: 65% heterosexual (up from 53% for same period in 2007), 20% MSM, and 12% injected drug users.

****Cumulative total of reported HIV cases = 5,243; migrants figured prominently among heterosexual cases; there was an increase among MSM and among heterosexuals but a decline in HIV related to IV drug use (of 36 cases 25 were Irish); and 28 new AIDS cases and 3 deaths.

AIDS, due to HIV (human immuno-deficiency virus²⁹⁴²) infection and its complications, causes many psycho-neurological syndromes: delirium, dementia²⁹⁴³, depression²⁹⁴⁴, mania²⁹⁴⁵, paranoid psychoses,

²⁹⁴¹ 146 were acquired heterosexually, of which 87 were born in sub-Saharan Africa.

²⁹⁴² Mostly HIV-1, discovered in 1986. HIV-1 is related to the harmless simian immunodeficiency virus. HIV-2, related to the sooty mangabey monkey virus, causes some cases in West Africa. The human disease may have come from western equatorial Africa during the 1930s. It may have crossed the species barrier because of eating monkeys or being injured by them.

²⁹⁴³ A subcortical dementia; the term AIDS-dementia complex (a ‘complex’ of dementia, motor, and behavioural aspects) has been replaced by AIDS- or HIV-1 associated dementia complex, and ‘AIDS-related complex’ or ARC is now called ‘symptomatic HIV infection’. A milder form of this disorder is called mild cognitive/motor disorder (MCMD) and is characterised by easy forgetting, problems with word-finding and general intellectual slowness. Not all cases of MCMD develop HIV-1 associated dementia complex.

²⁹⁴⁴ ECT has been used in AIDS patients for major depression and for the uncommon HIV-associated stupor.(Foster & Everall, 2007, p. 487) Depression has been blamed on abacavir, nevirapine (also causes vivid dreams), efavirenz (also associated with PTSD), and aciclovir. Lamivudine and indinavir can also disturb mood.(Foster & Everall, 2007, p. 489)

²⁹⁴⁵ Mania may be due to pre-existing bipolar disorder, organic disorders, or treatment (zidovudine, didanosine, and efavirenz). The term ‘AIDS mania’ refers to mania in late-stage HIV infection which is not thought to be related to bipolar disorder: patients are

schizophrenia-like psychosis, and (on hearing that one has AIDS or is seropositive) bereavement/adjustment reactions – in fact, adjustment disorder occurs in perhaps 90% of cases. Psychosis has occurred with abacavir, efavirenz and nevirapine. High suicide rates have been reported in HIV-infected patients, although rates may have fallen since the introduction of HAART (highly active antiretroviral therapy).²⁹⁴⁶ If HAART is commenced before onset of significant immunosuppression then the likelihood of progression to AIDS is much diminished. Past history of drug abuse may be associated with increased likelihood of psychosis in HIV infected patients despite no current substance use. (Sewell ea, 1994) Neuropsychiatric symptoms in patients with AIDS may be due to direct HIV effects on the brain²⁹⁴⁷ or the effects on the brain due to immunodeficiency²⁹⁴⁸.

AIDS: brain microscopy

Pallor of myelin in white matter

Cytomegalic-like lesions in grey matter²⁹⁴⁹

Multinucleate giant cells containing the great majority of detectable HIV RNA

Certain amount of macrophage infiltration, particularly of the leptomeninges and perivascular spaces

Mild inflammation (reactive astrocytosis and focal necrosis)

Mild to moderate cortical atrophy²⁹⁵⁰

Excess involvement of the basal ganglia, hypothalamus, thalamus and brainstem

AIDS: clinical categories²⁹⁵¹

CD4 cell count per Micro L	Clinical categories		
	A	B	C
500 +	A1	B1	C1
200-499	A2	B2	C2
<200	A3	B3	C3

Tuberculosis has developed in AIDS cases and may present in unusual forms, e.g. skin nodules, acute pericarditis with cardiac tamponade, cold abscess of the chest wall, and cerebral abscess.

The minority of paediatric cases are infected postnatally, e.g. via a blood transfusion.²⁹⁵² Most cases acquire HIV in utero or perinatally (e.g. via breast milk²⁹⁵³). About three out of four cases develop a

irritable and suspicious rather than 'high'; they are severely insomniac and therefore seem confused; HAART may need to be modified and the usual treatments for bipolar disorder (except valproate because it increases the risk of marrow damage in combination with zidovudine) may be required.

²⁹⁴⁶ A Swiss study (Keiser ea, 2010) found increased suicide risk to be associated with older age, male sex, injection drug use, and advanced illness whereas higher CD4 cell counts were associated with lower suicide rates.

²⁹⁴⁷ E.g. acute meningoencephalitis in the earliest stage and subacute encephalopathy later.

²⁹⁴⁸ Malignant lymphomas (non-Hodgkin's lymphoma large B cell type [strongly associated with Epstein-Barr virus] has become more common than Kaposi's sarcoma; also squamous carcinoma of cervix and anus [associated with human papillomavirus]), cerebral Kaposi's sarcoma (first described 1872 – proliferating vascular endothelial cells; caused by herpes virus 8), toxoplasmosis, cryptococcal meningitis, herpes simplex or cytomegalovirus encephalitis, hypoxia, treatment-related metabolic problems, idiopathic thrombocytopenic purpura, nonbacterial thrombotic endocarditis, and the Ramsay Hunt syndrome with facial palsy and clonic facial spasms. With improved survival rates, **distal sensory neuropathy**, due to HIV or antiretroviral agents, has become a major problem since 1 in 3 cases suffer from it. There are pain, tingling, and burning of the soles of the feet. Patients may become demoralised. Treatment involves stopping causative drugs, cessation of alcohol intake, management of any other disorder (e.g. diabetes or depression), and reducing pain levels (e.g. analgesics, TCAs, anticonvulsants such as lamotrigine).

²⁹⁴⁹ **Cytomegalovirus** (CMV) may cause subacute encephalitis characterised by headache, pyrexia, apathy, impaired attention, memory dysfunction, and ataxia. Inclusions may be seen in microglia and macrophages. Retinitis may impair vision. Ganciclovir and foscarnet are used in treatment.

²⁹⁵⁰ There is significant loss of neurones in the cerebral cortex, especially in frontal areas. Neurones are also lost in putamen, substantia nigra, and nuclei of cerebellum.

²⁹⁵¹ **Clinical categories:** A = no symptoms, acute HIV reaction, or persistent generalised lymphadenopathy – there may be transient peri-seroconversion symptoms; B = various symptomatic disorders, e.g. thrush, prolonged diarrhoea or pyrexia, or buccal hairy leucoplakia (caused by EBV), etc; C = AIDS (neurological involvement, progressive multifocal leucoencephalopathy, and cerebral *Toxoplasma gondii* infection). These are based on the Centers for Disease Control and Prevention 1993 classification.

²⁹⁵² Donated blood in the USA has been screened for HIV-1 since 1985 and for antibodies to HIV-2 since 1992, leading to a very diminished risk [<0.001%] risk of transmission of HIV. Paying blood donors in Peru led to an outbreak of HIV in infants – paid donors may not admit to risky behaviour.

progressive encephalopathy and/or microcephaly. Rarely this is caused by cytomegalovirus or primary brain cell lymphoma. Direct HIV damage is the usual mechanism. The classical picture is one of psychomotor retardation sometimes with behaviour problems. According to Cutting, (1992) HIV is transmitted in breast milk but the risk of neonatal death from not being breast fed (diarrhoea, respiratory infection) in developing countries may be greater than from HIV. Others recommend that mothers bottle-feed their infants. (APA, 2002, p. 150) Lymphocyte culture may be used to isolate HIV because antibody tests may remain positive (passive transfer from mother) for up to a year and a half after birth. Injection of cocaine and the exchange of sex for 'crack' was associated with a great increase in HIV and AIDS in the Americas a decade ago. (Farrell, 1991) Prostitutes are at very high risk for contracting HIV and are less likely to use condoms for non-paying clients; also, the partners of prostitutes may have had unprotected sex with other people, including homosexual encounters. In fact, only a minority of people who engage in high risk sexual activity use condoms consistently. (Steiner ea, 2008) Older people may be relatively unaware of STDs and be more likely to practice unprotected sex. (Bouman 2008, p. 690)

Comparison of first time treatment-seeking heroin users in Dublin (Long ea, 2006)

Inner city v suburban

Inner city – older, more HIV and hepatitis C, use of cocaine and regular heroin use

Authors' hypothesis: HIV therefore associated with area of residence and cocaine use?²⁹⁵⁴

Early, unrepresentative studies were considered to have overstated the risk of dementia and less than 5% of cases becoming demented are considered realistic, most cases developing it late in the course of the disorder. Problems with planning, problem solving, sequencing and concept formation were, however, noted to be common in advanced cases of AIDS.

Psychotic patients may be deluded nowadays that they have been given AIDS deliberately. People with depressive or obsessional personalities may worry excessively about AIDS²⁹⁵⁵. Such people may present with chronic anxiety, depression, or even conversion symptoms. Many of these symptoms may mimic the prodromal states of AIDS. Psychopaths with AIDS may present special management problems.

All cases have positive serology by 6 months, most being positive by 12 weeks, some as early as a fortnight. Patients with AIDS dementia have a positive ELISA²⁹⁵⁶ test. Confirmation is by way of Western blot.

HIV needs three enzymes to reproduce within the host: reverse transcriptase, protease, and integrase.

Antiretroviral drugs²⁹⁵⁷

<i>Group</i>	<i>Examples</i>	<i>Some adverse effects</i>
Nucleoside reverse transcriptase inhibitors (NRTIs) ²⁹⁵⁸	Abacavir, Didanosine, Emitricitabine, Lamivudine, Zidovudine, Zalcitabine	Anaemia, cardiomyopathy, fat loss (extremities), hepatic steatosis-lactic acidosis, myopathy, neutropenia, pancreatitis, peripheral neuropathy
Non- nucleoside reverse	Delavirdine, Efavirenz,	Bleeding (in haemophiliacs),

²⁹⁵³ Being breastfed only during the first 6 months of life may carry less risk of acquiring HIV than being breastfed and given other food/liquid. (Holmes & Savage, 2007)

²⁹⁵⁴ Other possible explanations include IV habit and needle-sharing!

²⁹⁵⁵ So-called AIDS-phobia, AIDS panic or pseudo-AIDS syndrome: some of these patients have problems accepting sexual orientation or with sexuality in general, or they may have negative religious or cultural sexual beliefs, and they may be guilty about past sexual 'rule-breaking'.

²⁹⁵⁶ Enzyme-linked immunosorbent assay.

²⁹⁵⁷ Up to date treatment guidelines are available at www.BHIVA.org.uk (UK) and <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> (USA). Potential drug interactions are found at www.hivdruginteractions.org (Liverpool, UK).

²⁹⁵⁸ Abacavir and didanosine may increase risk for myocardial infarction. (D:A:D Study Group, 2008)

transcriptase inhibitors (NNRTIs)	Nevirapine	deranged hepatic enzymes, fat redistribution, GIT intolerance, hyperlipidaemia, insulin resistance-hyperglycaemia Efavirenz can cause delirium depression, insomnia, vivid dreaming, dizziness, and poor concentration Efavirenz and Nevirapine decrease methadone ²⁹⁵⁹ levels by half (can precipitate abstinence)
Protease inhibitors (PIs)	Amprenavir ²⁹⁶⁰ , Atazanavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir	Hepatitis, rash (Stevens-Johnson)
Others	Raltegravir, Enfuvirtide, Tenofovir	

AZT (zidovudine²⁹⁶¹), which inhibits viral reverse transcriptase²⁹⁶², prevents AIDS dementia in many cases. AZT can suppress bone marrow. It can also cause headache, insomnia, and restlessness. Modern anti-HIV therapy involves reverse transcriptase inhibitors like AZT and lamivudine protease inhibitors such as indinavir. The non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz have been reported to cause psychosis.(Wise, 2002) There is increased sensitivity in patients infected with HIV to the EPS and anticholinergic side effects of high-potency and low-potency antipsychotic drugs respectively.(APA, 2002, p. 210)

Raltegravir (Isentress), an HIV-1 integrase inhibitor, prevents the virus integrating its genetic material into additional healthy cells during the early phase of cell infection.

The combination of darunavir and ritonavir is promising.

Histone deacetylation is important for quiescence of HIV gene expression in infected resting CD4+ T lymphocytes. Blockade of histone deacetylase 1 leads to increase in HIV. Valproic acid inhibits histone deacetylase and seems to accelerate clearance of HIV from resting CD4+ T lymphocytes.(Lehrman ea, 2005)

A stable partnership may delay progression to AIDS or death in HIV infected patients receiving highly active antiretroviral therapy (HAART²⁹⁶³).(Young ea, 2004) How it does so is not answered by this research (adherence, less depression?). Quiescent CD4 cell provirus reservoirs in HAART-treated cases may potentially prevent total viral eradication. Resistance to anti-HIV drugs is a worry (UK Group on Transmitted HIV Drug Resistance, 2005) as are reports of HIV patients developing florid leprosy lesions during the initial months of antiretroviral therapy.(Lawn & Lockwood, 2007)

Exclusive sexual abstinence only programmes do not appear to affect HIV risk in wealthy countries (Underhill ea, 2007) although methodological problems are common in such research.

Work on the development of a vaccine for HIV-1 remains disappointing.(Buchbinder ea, 2008; Reks- Ngarm ea, 2009)

Multiple sclerosis (MS)²⁹⁶⁴

²⁹⁵⁹ **Methadone** levels are reduced by ritonavir (including in combination with lopinavir), nevirapine, fosamprenavir, amprenavir, efavirenz, and nelfinavir. Methadone increases concentration of zidovudine and reduces levels of stavudine and didanosine.

²⁹⁶⁰ Do not give amprenavir with disulfiram or metronidazole.

²⁹⁶¹ Or azido-deoxythymidine.

²⁹⁶² Preventing transcription of RNA to DNA and its subsequent insertion into the host genome.

²⁹⁶³ A mixture of inhibitors used to counter emergence of resistance.

²⁹⁶⁴ **MS** is a chronic demyelinating disease of complex aetiology described by Charcot that occurs mainly in temperate climates. It is rare within 23° north and 23° south. Insufficient exposure to ultraviolet radiation in childhood may have an aetiological role.(van der Mei ea, 2003) MS seems to be more common in people born in May and to be less common in those born in November.(Willer ea, 2005) The offspring of low-risk immigrants may develop a similar prevalence of MS to that of their adoptive country, but migrants to South Africa who were older than 15 years retained the high incidence of their birthplace (i.e. the environmental risk may operate in

MS is probably independent of trauma or other illness, although an increase in life events or marked chronic difficulties compared to controls in the 6 months prior to clinical onset has been reported. Premorbid personality is probably normal in most cases. Hysteria is the classical misdiagnosis, and hysterical reactions may complicate MS. Some authors have stressed a tendency to bottle up feelings and others report an unhappy childhood, while still others state that MS patients were always tense and anxious and had immature personalities. Some relapses may coincide with emotional trauma and others do not.

MS

Only 18% have an affected first degree relative

Concordance for MS is higher in MZ than DZ twins: 25-50% v 2-17% in different reports

Susceptibility locus on chromosome 6 has been suggested

Increased frequency of HLA-B7, HLA-A3, HLA-Dw2 and especially HLAD2

Comparison of full-sib and half-sib (one biological parent in common) shows that halving the number of potentially contributing genes lowers the risk of MS by a factor of 2.62 (may favour polygenic hypothesis)

MS has been linked to many chromosomes with little replication

Gene variants IL7R-alpha (IL-7 gene) and IL2R-alpha (IL-2 receptor) increase risk of developing MS by 20-30% (see International Multiple Sclerosis Genetics Consortium, 2007)

Link consistently shown with MS with extended haplotype of the MHC²⁹⁶⁵, especially those containing HLA-DRB1*1501 (Dyment *et al.*, 2004)

Depression²⁹⁶⁶ is commoner early on, euphoria appearing later

No real proof that depression is reactive and euphoria is biological – complex in reality

Mood symptoms do not correlate well with disability

Depression is more common with cerebral than with spinal lesions

Temporal lobe involvement may be a risk factor for depression (Schwid *et al.*, 2000)

Fatigue (mechanism obscure) and pain (often widespread and chronic²⁹⁶⁷) are very common in MS

A few cases present with cognitive impairment, which may be the only manifestation of MS

Organic personality change may lead to emotional shallowness or apathy

Overall psychometric performance correlates with measures of severity on MRI

Widespread cognitive deficits with sparing of naming ability and relative preservation of verbal memory

adolescence). MS usually begins between 20-40 years and is very rare before adolescence or after 50 years. It may be slightly more common in women. The prevalence in Northern Ireland in 1987 was 104 definite cases/100,000 of the population. A slow virus (or the measles virus) affecting children has been suggested.

Common early manifestations of MS are ataxia, diplopia, vertigo, other brainstem problems, optic neuropathy consisting of optic neuritis (nerve head – swollen disc) or retrobulbar neuritis (further back – ‘patient cannot see and examiner cannot see’, i.e. fundus appears to be normal), and impaired sensation in lower limbs, and paresis of the limbs. Other problems include intention tremor, nystagmus, impaired colour vision, slurred or scanning speech, urinary incontinence, impotence, seizures, impaired vibration and position sense, hyperreflexia, paraplegia, and extensor plantar responses. Uhthoff’s phenomenon consists of a temporary return of symptoms of acute optic neuritis another illness, temperature change, physical exertion, or other stress; it does not suggest relapse. Lhermitte’s sign is a tingling sensation in the back or limbs on neck flexion. Apart from Lhermitte’s sign, other suggestive findings include worsening of symptoms with exercise or fever, onset before age 50 of trigeminal neuralgia, and recurrent VII nerve paralysis. Treatment of exacerbations is with ACTH and steroids (e.g. IV methylprednisolone followed by prednisone). Longterm steroid treatment carries no clear benefit and has considerable side effects. Prophylaxis for steroid induced mania has taken the form of lithium or low dose neuroleptics. Carbamazepine, although often used for manic attacks, can potentially exacerbate the symptoms of MS, possibly by blocking sodium ion channels. A modest reduction in frequency of episodes has been reported with the various interferons, interferon-beta-1b (but probably not interferon-beta-1a) being capable of causing severe depression and suicide (it is sometimes given with prophylactic SSRI – the literature on the association between depression and beta-interferon is mixed: no increase, increase, and decrease: Carson *et al.*, 2007, p. 345). Glatiramer acetate is another disease-modifying drug with modest effects, with a substantial minority of cases showing a less than optimal response. Immunosuppression with drugs such as azathioprine and methotrexate may be needed for the most progressive cases. Mitoxantrone is a chemotherapeutic drug for non-responsive cases which may cause cardiomyopathy or acute leukaemia. Natalizumab stops T lymphocytes crossing the blood-brain barrier; it can induce progressive multifocal leucoencephalopathy (PML). Rituximab and alemtuzumab can cause PML and thrombocytopenia respectively. (Hutchinson, 2008)

²⁹⁶⁵ Major histocompatibility complex (HLA, human leucocyte antigen) of 140 genes on chromosome 6.

²⁹⁶⁶ ECT is usually safe in MS cases except perhaps if there are gadolinium-enhancing plaques seen on MRI, the latter indicating disease activity.

²⁹⁶⁷ There are many possible mechanisms, e.g. spasticity or dysesthesia, the latter being helped by amitriptyline or gabapentin. Trigeminal neuralgia is an acute manifestation of MS.

Psychoses may be secondary or incidental

Sometimes misdiagnosed as hysteria and the vulnerable may develop an hysterical response

One theory of causation states that anxiety excites a vascular response. Most such theories are highly suspect. Smoking is associated with increased risk for MS and may also accelerate conversion from a relapsing-remitting to a progressive course.(Healy ea, 2009) All degrees of dementia have been reported, especially with defects of memory and speech. Air encephalography revealed enlarged ventricles and increased air collection over the hemispheres. CT scans may show plaques as areas of low density. Alternatively there are high-density areas enhancing with contrast during an acute relapse. MRI is superior to CT.²⁹⁶⁸ Plaques are most common near the ventricles. Rate of progression of dementia is very variable, being fulminant in some cases. When testing visual evoked responses it is normal to get a major downward (positive) wave at about 100-msec (P100). Demyelination of the optic nerve delays this wave with relative preservation of its form. CSF may contain myelin basic protein, oligoclonal bands, and an increase in the percentage of gamma globulin. Depression appears to be predicted by multiple interacting variables, especially trait anxiety and functional status but also alexithymia and level of satisfaction with social support system.(Gay ea, 2010) Depression may respond to SSRIs and supportive or problem-solving psychotherapies. Abnormal laughing or crying may respond to amitriptyline. Amantadine or modafinil may improve fatigue; other approaches include aerobics, rest periods, and heat avoidance. Baclofen²⁹⁶⁹ reduces spasticity. There is some evidence that oral cannabinoids may also be useful for spasticity (Zajicek ea) but they should only be employed if legal, available, if other treatments do not work, and if the patients desists from driving.(Metz & Page, 2003) Donepezil (Greene ea, 2000) and training in compensatory strategies may be helpful for cognitive problems. Thalidomide (Thalidomide Pharmion) because available in 2008 for MS with strict precautions against use in pregnancy. Vitamin D may reduce the risk of relapse.

Progeria²⁹⁷⁰

This is a rare, sporadic, autosomal dominant syndrome.(Korf, 2008; Merideth ea, 2008) A child is born apparently in normal health but stops growing before the third birthday. Many of the changes of senility develop and the end state is eventually reached. All cases end up looking like one another²⁹⁷¹. Lamin A (progerin) truncation²⁹⁷² has been reported (De Sandre-Giovannoli ea, 2003) causing nuclear membrane disruption and altered transcription.

Adult progeria²⁹⁷³

This is excessively rare and may possibly be inherited as an autosomal recessive trait. The gene responsible encodes a helicase enzyme that unpairs DNA strands.(Yu ea, 1996) It can affect the siblings of both sexes. It is possibly a caricature of normal ageing. There is shortness of stature. The average life span is 47 years. Up to 10% of cases develop mesenchymal neoplasia. There are various associated physical defects. Many of the cases have been reported in Japan, but it can occur elsewhere. Some cases have been mentally retarded or had cerebral cortical atrophy.

Cysts of the third ventricle

Colloid cysts are usually silent until the third to fifth decades of life. They may cause delusional depression, delirium, dementia, neurotic syndromes, and schizophrenia-like psychosis. Neurological findings include cranialgia²⁹⁷⁴, papilloedema, false localising signs, increased intracranial pressure, gastrointestinal upset, fainting, diminished level of consciousness, and sudden death due to acute obstruction of CSF.

²⁹⁶⁸ However, use of MRI to confirm MS on the basis of one neurological episode may lead to over-diagnosis and over-treatment.(Whiting ea, 2006) Most lesions are bright on T2-weighted MRI and are best seen with fluid-attenuated inversion-recovery (FLAIR) MRI.

²⁹⁶⁹ Baclofen can cause GIT upset, drowsiness, delirium, and seizures.

²⁹⁷⁰ Hutchinson-Gilford syndrome, Hutchinson being best remembered for the abnormal incisors in syphilis.

²⁹⁷¹ The child does not thrive in the early months of life, remaining small with very little body fat; as the child ages the skin becomes thin and sclerotic, the hair is lost, and osteoporosis and deteriorating cardiac function develop; death usually occurs in the early teens from myocardial infarction.

²⁹⁷² Change from glycine GGC to glycine GGT in codon 608 of the lamin A (LMNA) gene. Lamin A is part of the protein network forming the nuclear lamina inside the nuclear membrane.

²⁹⁷³ Werner's syndrome or segmental progeroid was described by Otto Werner in 1904.

²⁹⁷⁴ Headache may be episodic positional due to cyst on a stalk moving in and out of foramen of Monro.

Akinetic mutism was described by Cairns *et al.* (1941) in a patient with an epidermoid cyst of the third ventricle. This syndrome may occur with midbrain or posterior diencephalic lesions.²⁹⁷⁵ Cystic tumours can be aspirated, which may reverse mutism, although the patient will be unable to remember anything for the time when mute.

Other causes of dementia

These are numerous and include:

Limbic encephalitis - paraneoplastic or primary autoimmune phenomenon²⁹⁷⁶

Boxing injuries to the head

Behcet's syndrome²⁹⁷⁷

Buerger's syndrome²⁹⁷⁸

Polycythaemia rubra vera²⁹⁷⁹

Sarcoidosis

Thalamic degeneration – rare

Subacute sclerosing panencephalitis

Myotonic dystrophy²⁹⁸⁰ - a minority of cases become demented

Polyarteritis nodosa²⁹⁸¹

Cranial arteritis

MELAS syndrome²⁹⁸²

Myoclonic epilepsy with ragged red fibres²⁹⁸³

Sneddon's syndrome²⁹⁸⁴

Cerebrotendinous xanthomatosis²⁹⁸⁵

Granulomatous angiitis²⁹⁸⁶

Cerebral amyloid angiopathy²⁹⁸⁷

²⁹⁷⁵ Late stage normal hydrocephalus may be complicated by akinetic mutism.

²⁹⁷⁶ Paraneoplastic cases are associated with such conditions as small cell lung cancer or seminoma of testis. In such instances it is thought that antibodies against cancer cells (e.g. antiHu) cross-react with normal nerve cells. Primary cases have antibodies to voltage-gated potassium channels; most have no cancer but a few have thymoma; treatment-resistant seizures and hyponatraemia are common; episodic memory is dysfunctional; MRI shows abnormal high temporal lobe signal; EEG often has focal temporal lobe abnormalities; and management includes high dose steroids, plasma exchange, or IV immunoglobulin.

²⁹⁷⁷ **Behcet's syndrome** is found most often in young males. There is often a family history of the disorder, with autosomal recessive transmission in childhood-onset cases. The HLA-B region is associated with the syndrome. Ulcers of the mouth and genitalia and eye problems (e.g. uveitis and retinal vasculitis – sometimes with permanent blindness) occur in episodes over a number of years. Arthritis, erythema nodosum, and thrombophlebitis may be present. CNS involvement may cause fever, stiff neck, headache, and various neurological signs, including brainstem signs such as cranial nerve palsies and diplopia. Other reported neurological effects were dysexecutive syndrome, memory problems, periods of confusion, dementia, psychosis (bipolar or schizoaffective), and dural sinus thrombosis. Pathological findings in cases with CNS involvement include relatively mild perivascular inflammation and areas of infarction, demyelination, and necrosis.

²⁹⁷⁸ **Thromboangiitis obliterans** – described in Leo Buerger (1879-1943, born Austria) in 1908 - found in male smokers (usually in 20s-40s) – rarely affects brain: headache (migraine-like), seizures, and dementia.

²⁹⁷⁹ **Polycythaemia rubra vera**: myeloproliferative disorder with excess red (and usually white and platelet) cells; plethoric facies; increased viscosity of blood; headache, blurred vision, vertigo, delirium, cerebral TIAs, infarction, dementia.

²⁹⁸⁰ Chromosome 19q13 (gene is called DMPK-3'UTR, dominant inheritance, triplet repeat, myotonin kinase produced) usually presents in adults: myotonia (despite weakness, the muscles are difficult to relax, e.g. the patient grasps your hand but cannot let go of it), facial myopathy (lower lip droops, ptosis), distal muscle atrophy, cataracts, and frontal baldness. Hypersomnia is common and patients may sleep for very long periods.

²⁹⁸¹ This rare condition affects small and medium sized arteries (including nutrient arteries). It usually starts in mid-life. Many organs may be affected. Neurological effects include peripheral neuropathy, encephalopathy, cerebral/subarachnoid haemorrhage, damage to cranial nerves, a mass effect from necrotic brain tissue, and delirium. Subcutaneous nodules may be found. Diagnosis, such as skin, kidney or nerve, is confirmed by biopsy.

²⁹⁸² Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes: inherited from mother – usually presents in childhood.

²⁹⁸³ **Myoclonic epilepsy with ragged red fibres** is a mitochondrial myopathy with myoclonic epilepsy, dementia, cerebellar ataxia, nerve deafness, and (not all cases) optic atrophy and peripheral neuropathy. Muscle biopsy shows ragged-red fibres and abnormal mitochondria. Age of onset and clinical severity varies because of heteroplasmy. Many abnormal mutations of mitochondrial tRNA genes have been discovered.

²⁹⁸⁴ Livedo reticularis, strokes, and, in some, dementia.

²⁹⁸⁵ Dementia, tendon enlargement, cataracts, and ataxia.

²⁹⁸⁶ Idiopathic, possibly autoimmune reaction to a virus.

²⁹⁸⁷ Congophilic amyloid angiopathy: mostly sporadic; autosomal dominant forms include the Dutch (APP gene mutation) and Icelandic (latter due to mutation in CST3 gene encoding for the enzyme-inhibiting Cystatin C protein) types. It is more common in

Pure hippocampal sclerosis²⁹⁸⁸
 Neurocysticercosis²⁹⁸⁹
 Cerebral toxocariasis²⁹⁹⁰
 Dialysis
 Malabsorption
 Alcoholism

APP is cleaved to produce the A β peptide, the chief component of AD plaques. A mutation in APP (Glu693Gln) was reported in those few families in the Netherlands with hereditary cerebral haemorrhage of the Dutch type (recurrent cerebral bleeding due to excess A β deposition in brain blood vessel walls – this research showed that APP mutation could cause A β deposition and encouraged research into APP mutation in families with early-onset AD).

Worster-Drought syndrome

Familial British dementia; autosomal dominant; described in 1930s; presenile dementia, spastic paraparesis, and cerebellar ataxia; MRI shows deep white matter lesions and lacunar infarcts; prominent cerebral amyloid angiopathy and AD-like plaques and tangles; however, deposited amyloid is negative for antibodies against the β -amyloid found in AD (Dermaut & Van Broeckhoven, 2002)

Familial Danish dementia

Heredopathia ophthalmoto-encephalica; abnormally long APP; cataracts, deafness, progressive ataxia, and dementia with AD-like neuropathology (Vidal ea, 2000)

Nasu-Hakola disease

Presenile dementia with bone cysts of ankles and wrists; 19q13; rare recessive disorder found mainly in Finland and Japan (Dermaut & Van Broeckhoven, 2002)

The **Mini-Mental State Examination** (MMSE, Folstein ea, 1975) is the commonest bedside cognitive test used by clinicians. (see box) Education can influence scores, necessitating lower cut-off scores. (Nixon & Albert, 1999) The cut-off point is less than 24/30. The MMSE does not reliably discriminate mild dementia (ceiling effect) or severe dementia (floor effect). Early cognitive decline may be missed in people with a high IQ. The MMSE is more useful for tracking cortical than subcortical (including HIV-associated²⁹⁹¹) dementias. (Rao ea, 1991) Neither does it distinguish dementia from delirium and some delirious patients score in the normal range. It is not sensitive to executive dysfunction or every cognitive problem (e.g. dyspraxia). As with other screening tests of cognitive disorder, the predictive value of the MMSE when one moves out of the clinic and into the community²⁹⁹². (Brayne & Calloway, 1991)

Some tests for cognitive impairment

(a) The Mini-Mental State Examination (MMSE)

Patient..... Age years

Examiner..... Time am-pm

Date.....

Clinical problem.....

Max.
Score Score

(1) Orientation

What is the year/season/date/day/

females and with increasing longevity. Finnish type familial amyloidosis results from GSN gene mutation that codes for the actin-binding protein gelsolin.

²⁹⁸⁸ This consists of severe cell loss and gliosis in the hippocampus, unknown aetiology, usually in advanced age, and prominent short-term memory loss.

²⁹⁸⁹ *Taenia solium* (in infected meat), especially in poor countries, rarely affects CNS (neurocysticercosis), focal neurological signs, hydrocephalus, personality change, seizures, anaemia, worms in stool, space-occupying lesions on CT or MRI, serological tests, treat with antihelminthics such as albendazole and treat complications (e.g. steroids for increased intracranial pressure or anticonvulsants for seizures).

²⁹⁹⁰ *Toxocara canis* (do roundworm), eosinophils in blood and CSF, positive antibody titre, and treat with drugs such as albendazole.

²⁹⁹¹ The *HIV Dementia Scale* (Power ea, 1995) may be used for this disorder.

²⁹⁹² The case:non-case ratio falls as one moves away from the clinic.

month?	5	()
Where are we? (country/county/town/ e.g. hospital/floor)	5	()
(2) Registration		
Name any three items (1 sec. each). Repeat all three. Give 1 point for each correct answer. Now repeat them until learned. Count all trials and record.	3	()
Trial		
(3) Attention and calculation: Serial 7s (i.e. 100, 93, 86 etc). 1 point for each correct. Stop after 5 answers. * Alternatively, spell 'would' (or 'world') backwards. **	5	()
(4) Recall: Ask for the 3 objects as in (2). Give 1 point for each correct answer.	3	()
(5) Language		
Show a pencil and watch (name them). (2 points).		
Repeat the following: 'No ifs, and or buts'. (1 point).***		
Follow a 3-stage command: 'Take a piece of paper in your right hand, fold it in half, and put it on the desk'. (3 points).		
Write: 'Close your eyes', and ask him to read and obey. (1 point).		
Write a sentence (noun and verb). (1 point).		
Copy design – 2 partly overlapping 5-sided figures. (1 point).		
(Look for where sides cross and correct number of angles).	9	()
RECORD TOTAL SCORE OUT OF 30		
What is his level of consciousness along this continuum (Alert, drowsy, stupor, or coma)?		
The total can be brought up to 40 points by adding tests that mainly test right hemisphere function:		
(1) Draw a triangle, square and circle, or construct three shapes with matches (3 points).		
(2) Draw a clock face, filling in numbers (take off one point for each error) (2 points).****		
(3) Cross each of random lines shown in a square (subtract one point for each omission) (5 points).		

*93, 86, 79, 72, and 65: score total number of correct answers. **Score number of letters in correct order, e.g. 'dlrow' = 3.²⁹⁹³
 Another test of repetition would be the Babcock sentence: 'One thing a nation needs to be rich and great is a large, secure supply of wood'. *See Manos, 1999. The *Clock Drawing Test* is a good screen of executive function (e.g. a patient with a frontal lobe lesion might join the hands in the wrong place because he/she is 'stimulus bound'²⁹⁹⁴ to the time he/she has been asked to indicate, or put numbers outside the clock face); it can also detect neglect syndromes²⁹⁹⁵ (numbers may appear clustered on one side of the clock face).

(b) Test for Severe Impairment (scores in brackets for correct response)

Patient..... Age years
 Examiner..... Time am-pm
 Date.....
 Clinical problem.....

Motor performance – ask person to demonstrate use of comb (1), to put top on pen (1), write name (legibly – 1): total = 3
Language comprehension - ask person to point to his ear and to close his eyes (1 each), and to indicate red pen from red, blue and green pens (1), and repeat for green pen (1): total = 4
Language production – pointing at your nose ask patient what it is (1), the colour of two different pens held up consecutively (1 each), pointing at a key ask patient what it is (1): total = 4
Immediate memory – your open hand contains a clip and patient must say which hand it is in (by pointing - 1), with closed hand repeat question (1), with your hands moved behind your back (1): total = 3
General knowledge – ask how many ears you possess (1), ask patient to count your fingers (1), how many weeks in a year (1), ability to sing most of words of 'Happy Birthday' along with you (1): total = 4
Conceptualisation – which is odd one out (show 2 clips and a pen – 1), give a red pen and ask him to place it next to same-coloured pen (red and green pens on desk – 1), move clip from one of your hand to another several times and ask him which hand you will put it in next and after he responds put the clip in the correct hand [and if he is wrong tell him what hand you would put it in and ask him again which hand you would put it in next - 1]: total = 3
Delayed memory – show thread, clip and key and ask which one was not used already in the testing (correct if points to thread – 1): total = 1
Motor performance – thank patient for being with you and offer him your hand (if he shakes your hand – 1): total = 1
 Grand total = 24

Test for Severe Impairment (TSI) (Albert & Cohen, 1992) is used for severely cognitively impaired patients. It minimises reliance on verbal skills.

²⁹⁹³ It is important to realise that some languages do not include or concept of spelling, e.g. Mandarin.

²⁹⁹⁴ **Stimulus bound:** Dementing patients have problems shifting frames of reference. They become distracted by accidental impressions/events and cannot shift attention away from them.

²⁹⁹⁵ A patient with a right-sided stroke might, when drawing an object such as a horse, leave out the left side of the picture or, when asked to perform the *Trail Making Test* (join dots in sequence) neglect the left side of the exercise (not use dots on that side of the diagram).

Functional Assessment Staging (FAST) (Reisberg, 1986) consists of a 7-point scale with subdivisions, e.g. 1 = no subjective or objective difficulty and 7(f) = loss of ability to hold up head independently or the neck is contracted and immobile. FAST stage 7, which has 6 substages, represents over half of the potential duration of AD. FAST can track the progress of AD much further than the MMSE which suffers from a 'floor effect' (stage beyond which there is no further drop in the scores). FAST depends on carer testimony. Wise and Strub (1999) point out that the examiner should not only ask patients to remember 3 objects (verbal/dominant) but they should also ask them to recall 3 shapes (non-dominant hemisphere).

The **Dementia Rating Scale-2 (DRS-2)** (Jurica ea, 2001) tests attention, memory, reasoning, and construction. This brief test with a deep floor (taps low levels of function) employs a screening approach: moderately difficult items are presented first, allowing other items in that domain to be skipped if the patient passes. The DRS-2 can be used to track progress of AD.

The **Addenbrooke's Cognitive Examination**²⁹⁹⁶ (ACE) (Mathuranath ea, 2000) includes the MMSE as well as asking the subject to remember a name and address (a more difficult test of anterograde memory), questions about current events, verbal fluency tests, and more probing evaluation of language and perception.

Tests for causes of dementia

FBC, ESR, Hgb, TPHA, FTA, T4, Free T3, TSH, urea and electrolytes, calcium, B12, folate, CT and MRI scans, EEG, echoencephalography, arteriography, lumbar puncture (LP), etc - all tests need some degree of clinical justification on the grounds of cost-effectiveness, availability, likely results, and invasiveness.

Thyroid screening may be misleading in people on phenothiazines, antiparkinsonian drugs, or lithium.

CT gives poor delineation of the posterior fossa. Polycythaemia occurs in multi-infarct dementia and haemangioblastoma of the cerebellum. Macrocytosis (with raised MCV) is often seen in alcoholism.

Presenile dementia slows down most of the components of the visual evoked response. The responses of the visual system to appropriate repetitive stimuli are isolated from the background EEG using a computer technique known as averaging. This may prove to be of diagnostic value in psychiatry in the future. It has already found clinical use in the investigation of multiple sclerosis.

Epilepsy

Epilepsy²⁹⁹⁷, a seizure tendency symptomatic of a brain affection, follows a chronic course with repeated, unprovoked seizures. It is the commonest chronic neurological disorder.

International League Against Epilepsy definitions

Epileptic seizure = clinical manifestation thought to be due to an abnormal and excessive discharge of a set of brain neurones

Epilepsy = disorder with at least 2 epileptic seizures that are unprovoked by an immediate identifiable cause

Rarely if ever is the cause of epileptic centrencephalic²⁹⁹⁸. The seizure threshold is 50-100% higher in males than in females. Pseudoseizures (non-epileptic attack disorder or non-organic/non-epileptic seizures²⁹⁹⁹) are not discussed here except to state that the ultimate diagnostic procedure is videotelemetry.

5% of people have a seizure³⁰⁰⁰ at some point in their lives and 0.5% has epilepsy

²⁹⁹⁶ Cut-off of 83/100 = dementia.

²⁹⁹⁷ Gk, *epilambanein*, to lay hold of/to seize.

²⁹⁹⁸ An outdated term since spike and wave activity may have a cortical origin rather than arise from a subcortical pacemaker.

²⁹⁹⁹ There is no satisfactory term. Pseudoseizures must be distinguished from *self-induced seizures*, usually associated with childhood, wherein a person with epilepsy deliberately sets about inducing a seizure, e.g. by jumping up in down in front of the slats of a venetian blind; motivation varies from pleasure to coping with stress.

³⁰⁰⁰ A seizure is an abnormal cerebral neuronal paroxysmal discharge that produces events detectable by the patient and/or an observer.

Prevalence of active epilepsy in adults is 4-6/1,000³⁰⁰¹

80-90% of second seizures will follow within 1-2 years

Majority of those who develop epilepsy do so before their twentieth birthday, rendering them educationally vulnerable

70% cases of epilepsy are idiopathic/primary (theories include imbalance between GABA and glutamate or a kindling phenomenon where repeated subconvulsive stimuli eventually cause seizures)

70% cases of epilepsy are partial (focal), the remainder being generalised (*vide infra*)

70% of cases of partial epilepsy are complex partial (formerly 'psychomotor'), i.e. half of all cases of epilepsy; most such cases arise from temporal lobe foci, although any lobe may be involved in practice: the aura may indicate the lobe of origin; the electrical disturbance produces the characteristic symptoms by spreading to the temporal lobe

A significant number of epileptics drive without informing licensing authorities and against medical advice, often for financial reasons and to avoid social stigma. Polytherapy may promote accidents by impairing performance. A wide range of figures for relapse rates are to be found in different studies of people who have had a single seizure.³⁰⁰²

A normal interictal EEG does not disprove a diagnosis of epilepsy, many epileptics have a normal interictal EEG, and an abnormal EEG is not proof that an 'attack' was epileptic. The scalp EEG is usually normal during a simple partial seizure. The EEG during a complex partial seizure will show unilateral or bilateral epileptiform activity, especially in temporal or frontotemporal areas. Spike and wave formations are found in 2% of people who do not have epilepsy. An EEG may or may not be helpful after a first seizure in adults. CT should be ordered if there has been a clear partial seizure or if there are focal neurological signs. Functional imaging (PET/SPECT) can be used during an ictus and postictally to show hypermetabolism and hypometabolism respectively in the epileptic focus. Methohexitone can assist, especially when used with sphenoidal electrodes, to localise interictal spikes.

Anticonvulsants appear to be safe when co-administered with ECT. (Sienaert & Peuskens, 2007) Grand mal (tonic-clonic) epilepsy can be associated with depression³⁰⁰³ that responds to ECT³⁰⁰⁴ or to drug treatment.

A single fit of exogenous or endogenous origin does not produce the progressive and sustained relief of depression that is produced by a course of ECT. Precipitants of epilepsy include laughing (gelastic³⁰⁰⁵ - Gk, *gelastikos*, to laugh), startle, flickering light (photic), reading, fatigue, hunger, eating (Abenson, 1969), dehydration (including a hot bath), fever, and rare individual precipitants such as remembering a specific event or a particular body movement. These reflex epilepsies affect 1-6% of epileptics. Any modality can be affected but the visual system is most commonly implicated. Other precipitants of epilepsy include lack of sleep, emotional stress, infection, and alcohol or drug ingestion or withdrawal. Catamenial epilepsy³⁰⁰⁶ is epilepsy manifesting just before or during menstruation. (Herzog, 2000) Kindling is discussed elsewhere.

Epileptic psychoses

(a) with *disturbed consciousness*³⁰⁰⁷

³⁰⁰¹ It was suggested by Brainwave Ireland (founded 1967; 353+(0)1+4557500; 249 Crumlin Road, Dublin 12; info@epilepsy.ie; www.epilepsy.ie/index.cfm/spKey/about.html) and UCD Centre for Disability Studies in 2009 that 9/1,000 people aged over the age of 5 years in Ireland have treated epilepsy.

³⁰⁰² The risk of subsequent seizures after a first seizure in adulthood is highest for patients whose initial seizure occurs between midnight and 9 a.m. Risk of recurrence is three times higher for someone who is less age 50 years, who has a family history of febrile fits or seizures of any kind, and whose first fit occurs between midnight and 8 a.m. (i.e. usually during sleep). The rate of recurrence was significantly higher for patients with EEGs showing generalised or localised epileptiform activity. 20-30% of newly diagnosed epileptics will develop chronic epilepsy.

³⁰⁰³ Depression associated with an actual complex partial seizure comes and goes suddenly. Much rarer are pleasant ictal feelings.

³⁰⁰⁴ As may some epileptic 'cloudy states' or rages.

³⁰⁰⁵ This may also be a manifestation of seizure activity (complex partial). Such laughter is unlike normal laughter and is not usually viewed as being funny by an observer. *Hamartoma of the hypothalamus* may cause **gelastic seizures** as well as precocious puberty and aggressiveness; most cases are cognitively impaired, although at least some of this may be due to the seizures or their treatment. If the patient cries during laughter the term *dyscrastic seizure* (Gk, *dyskrasia*, bad mixture) may be employed.

³⁰⁰⁶ Catamenial (Gk. *katamēnia*, menstrual period) pneumothorax is another rare association with onset of a menstrual period.

³⁰⁰⁷ States following paroxysms, petit mal status, psychomotor or complex partial status, those not chronically related to seizures, delirious states.

(b) with *normal consciousness*³⁰⁰⁸

Traditional classification of mental problems of epilepsy

- (i) Postictal (following a fit)
- (ii) Interictal (between fits)
- (iii) Preictal (before a fit)
- (iv) Ictal (during a fit)
- (v) Peri-ictal (preictal + ictal + postictal)

Preictal problems represent prodromata that come on gradually and last from hours to days, e.g. irritability, tension, malaise, fatigue, low mood, and headache. A prodrome is more frequently encountered with localisation-related epilepsy but it may be seen with generalised epilepsy.

Ictal disorders of psychiatric importance include aura, automatism, and non-convulsive status epilepticus. The *aura* (a simple partial seizure) consists of premonitory symptoms of focal origin and lasts a matter of seconds. It results directly from abnormal electrical discharge, e.g. in complex partial seizures a strange sensation may arise in the epigastrium that ascends to the throat. Other symptoms include vertigo, tinnitus, odd or indescribable feelings in various body parts such as head (*cephalic aura*), genitals, special sense changes, intense emotion, micropsia/macropsia, déjà vu, jamais vu, depersonalisation, and a variety of complex hallucinations. There may be more than one symptom as part of an aura. A primary motor cortex focus may cause clonic jerking of muscles. Dystonic posturing may occur in some cases. Most *automatisms* occur during a seizure or during post-ictal delirium but some patients with simple partial seizures have such phenomena (e.g. deglutition or lip-smacking) when in apparently clear consciousness.

Postictal states may last 1-2 minutes and may consist, for example, of confusion (delirium), fugue, twilight state, or aggressiveness. Status epilepticus may be associated with more prolonged confusion and may be confirmed by EEG. Post-ictal psychoses commence after a short post-ictal lucid interval and resolve within a few days; they are the commonest of the epilepsy-associated psychoses; they are abrupt in onset; affective symptoms (especially agitation) accompany the psychosis; and a minority (15% after 15 years) go on to develop chronic interictal psychosis, especially those with severe seizures and structural change.

Factors that may feed into postictal states

Psychosocial (stigma)
 Early onset epilepsy (failure of fits to remit, frequent seizures, male sex, or left-sided lesions)
 Temporal lobe (especially bilateral) and other focal lesions
 Poor seizure control
 Genetic predisposition to epilepsy or psychiatric disorder or both
 Intellectual disability
 Acquired brain conditions like trauma
 Drugs (anticonvulsants, other drugs, and alcohol)
 Polypharmacy³⁰⁰⁹

According to Lambert et al., (2003, p. 1109) moderate alcohol intake by epileptic patients is acceptable.

Inter-ictal symptoms/disorders have been classified into mood (anxiety and/or depression – the commonest epilepsy-associated psychiatric problems), schizophrenia-like, behavioural/personality-related³⁰¹⁰, and dementia. Dissociative seizures are also included here. Earlier onset of interictal psychosis may be associated with generalised epilepsy, normal intellectual functioning and a family history of psychosis. (Adachi et al., 2010) ‘Seizure phobia’ refers to excessive fear of having further seizures. It may respond to CBT.

³⁰⁰⁸ The latter can be subdivided into those of (a) duration of less than three weeks, often periodic, e.g. dysphoric, manic, depressive, alternating psychoses with productive symptom, and (b) long duration (more than three weeks, paranoid, schizophreniform, manic-depressive, and dementia).

³⁰⁰⁹ The clinician should consider stopping an ineffective first anticonvulsant when the addition of a second drug controls seizures. (Mellers, 2009, p. 371)

³⁰¹⁰ This idea is less reputable than it was in the past.

Classifying epileptic seizures

Generalised (often no warning or the warning may be non-specific)

Focal/partial/local (often has a specific aura)

Unclassified

Focal (partial) epilepsy may become secondarily generalised.

Generalised epilepsy (convulsive or non-convulsive) includes idiopathic epilepsy (grand and petit mal epilepsy), congenital or perinatal epilepsy, metabolic or hypoxic epilepsy, traumatic cases, toxic cases, febrile³⁰¹¹, infection, and any cause of focal epilepsy.

Focal epilepsy is divided into temporal lobe³⁰¹² and focal motor (including Jacksonian³⁰¹³) epilepsy. The aetiology of focal epilepsy includes unknown (sometimes familial), and congenital or perinatal, tumour, haemorrhage, abscess, trauma, infection³⁰¹⁴, and hypoxic/ischaemic.

Benign childhood epilepsy affects children aged 3-16 years. It has a favourable prognosis. Presenting with simple partial seizures it may or may not progress to secondary generalised attacks. The EEG shows centrotemporal spikes.

The patient runs or walks in circles during a 'cursive' (complex partial) seizure. An 'ambulatory automatism' (semi-purposeful wandering/searching/'escaping') may occur as part of a complex partial seizure. Deviation of the head and eyes occur in '(ad-) versive' seizures (frontal lobe epilepsy³⁰¹⁵), and its lateralising significance is disputed³⁰¹⁶. (Moore, 2001, p. 331) *Epilepsia partialis continua* refers to persistent focal seizures (partial status). Complex partial seizure status refers to continuous complex partial seizures.

Epilepsy

Differential diagnosis

Organic - syncope, hypoglycaemia, transient ischaemic attacks, migraine, sleep disorders

Non-organic - temper tantrums, breath holding, hyperventilation, hysteria, panic attacks, schizophrenia, aggressive outbursts in an unstable personality, night terrors, malingering, and factitious disorder

Aetiology

Idiopathic/constitutional – the biggest group

Hereditary³⁰¹⁷/familial – petit mal, some cases of temporal lobe epilepsy (TLE)³⁰¹⁸, aminoacidurias, trisomy 21, lipidoses, mutations of voltage-gated channels/ligand-gated ion channels/neurotransmitter receptors

³⁰¹¹ Simple benign cases must be distinguished from fever-activated epilepsy.

³⁰¹² Partial *complex* cases involve spread and *loss of/disturbed consciousness*, the commonest type to see a psychiatrist; the other type is partial *simple* seizures – with *no impairment of consciousness*.

³⁰¹³ **John Hughlings Jackson** (1835-1911) who described this epileptic 'march' married his cousin Elizabeth Dade Jackson in 1865. She developed Jacksonian seizures! (Draaisma, 2009, p. 130) In fact, Louis-François Bravais of France had described the same manifestation of epilepsy before Jackson in 1827. Bravais lost out when Charcot named the phenomenon for Jackson! Jackson is best remembered for his idea of hierarchical arrangement of the nervous system: the last parts to develop (e.g. neocortex) inhibit older/lower parts and damage to newer areas lead to positive/release phenomena/gain of function (e.g. brisk jaw jerk) and/or negative/loss of function phenomena (e.g. paresis).

³⁰¹⁴ Especially herpetic.

³⁰¹⁵ Involvement of supplementary motor cortex leads to head turning and ipsilateral arm extension (*fencer's posture*).

Familial nocturnal frontal lobe epilepsy usually starts in adolescents or young adults with clusters of brief motor seizures (grunts/gasps/vocalising at first then thrashing movements or stiffness, with clonic jerks; 2-20 seconds in duration but sometimes longer;) during n-REM sleep. The patient awakens recurrently and shows stereotyped movements. Sleepwalking may occur and may be accompanied by unintelligible speaking or screaming. Patients may or not be aware that seizures have occurred and typically feel tired by day. The aura includes epigastric, sensory or psychological phenomena. Medication, such as carbamazepine, helps. It is inherited as an autosomal dominant trait. Different mutations are associated with *schizophrenia* (or just its negative symptoms), apathy, or intellectual retardation and/or behavioural problems. The affected genes are CHRNA4 (20q13.3) and CHRN2 (1q21).

³⁰¹⁶ However, others hold that upward eye deviation is found in generalised epilepsy and deviation away from the lesion/focus is found in focal epilepsy, especially if the frontal eye fields are involved. Eye movement direction is unreliable as a lateralising guide when the seizure emanates from a temporal lobe.

³⁰¹⁷ In many cases there appears to be many genes involved.

Developmental defects – phakomatoses, intrauterine (rubella, CMV, toxoplasmosis), irradiation

Birth trauma – perinatal anaemia, cerebral contusion, cerebral haemorrhage/thrombosis

Anoxia in infancy/childhood

Tumours – primary/secondary

Vascular – mature infarcts, A-V malformation

Infection – febrile convulsion (cf. text), viral encephalitis³⁰¹⁹, bacterial or TB meningitis, cerebral abscess, cysticercosis³⁰²⁰, neurosyphilis, echinococcus³⁰²¹, toxocariasis, toxoplasmosis

Inflammatory – SLE/PAN/MS

Metabolic – uraemia, water intoxication, low Na/Ca/Mg, hypoglycaemia

Toxic – alcohol, barbiturates, amphetamines, lignocaine, TCAs, phenothiazines, lead, etc (Kainic acid³⁰²² the related toxin in seafood, demioic acid, probably cause convulsions by inhibiting GABA neurotransmission.)

Degenerative – AD, CJD, Huntington's disease; *Rasmussen syndrome* consists of unilateral brain atrophy, continuous seizures, and cognitive decline arrested by removal of atrophic brain tissue.

Rare forms of epilepsy

Atypical absence – slower EEG, clinically like petit mal, of mentally retarded (Lennox-Gastaut syndrome, which sometimes follows on from West's syndrome), seizures often refractory

Tonic seizures – tonic posturing of limbs or trunk

Infantile spasms (West's syndrome) – brief and sudden head flexion – salaam attacks – often failure to develop – regression – onset 3-9 months – may be refractory, or may respond to vigabatrin, steroids and, if the latter do not work, a ketogenic diet (Hong ea, 2010)

Gangliosidosis³⁰²³

Myoclonic epilepsy³⁰²⁴ – (a) single or repetitive sudden convulsive movements of limbs/trunk; (b) mostly children with idiopathic epilepsy – early morning attacks; (c) photosensitivity myoclonus and epilepsy; and (d) hereditary myoclonic epilepsies – generalised seizures and myoclonus with degenerative disease, e.g. Lafora body disease (autosomal recessive familial disorder; children/adolescents with myoclonus, major seizures and dementia – death within a few years – polyglucosan-Schiff-positive intracellular inclusion bodies in brain, muscle, liver or skin eccrine sweat glands) – a (recessive) gene (Cystatin B-5'UTR) for progressive myoclonic epilepsy³⁰²⁵ has been mapped to 21q. Dravet's syndrome (severe myoclonic epilepsy of infancy, a progressive encephalopathic state) starts (often as febrile seizures initially) in infants and seems to be related to mutations in the sodium channel gene SCN1A

Juvenile myoclonic epilepsy (Janz syndrome) is linked to chromosome 6p (unlike benign familial neonatal convulsions³⁰²⁶ with genes mapped to 8q24 and 20q13.3) and presents in late childhood/early adolescence – myoclonic jerks (mainly early morning) +/- progression to generalised tonic-clonic attacks

Note: Myoclonic and atonic³⁰²⁷ (astatic seizure/drop attack) forms of epilepsy are difficult to control, but may respond to sodium valproate or clonazepam.

Acquired aphasia with epilepsy (Landau-Kleffner syndrome)

The cause is unknown, but encephalitis has been suggested. The child's language develops normally but later, usually at 3-9 years of age, it loses both receptive and expressive language, despite retention of general intelligence. The EEG is abnormal, usually with

³⁰¹⁸ **Autosomal dominant partial epilepsy with auditory features (autosomal dominant lateral TLE)** is due to mutations at 10q24. It is rare. There are simple partial seizures accompanied by auditory +/- visual hallucinations.

³⁰¹⁹ Encephalitis is more likely to be complicated by epilepsy than is meningitis and aseptic meningitis does not appear to be epileptogenic. Also, cerebral abscess leads to epilepsy in about a third of cases.

³⁰²⁰ Secondary to swallowing cestodes (tapeworms): Encephalitis may accompany heavy infestation. Most often cerebral problems are delayed by years when larvae die: epilepsy, ataxia, internal hydrocephalus, and change in personality: calcification of cysts in brain is not as marked as in muscle; x-ray of striated muscle/CT/MRI/biopsy of subcutaneous nodules/serology; treat with praziquantel and steroids; surgery for hydrocephalus.

³⁰²¹ Hydatid disease: brain cysts can cause focal seizures.

³⁰²² Systemic or intra-cerebral kainate injection causes long-lasting limbic seizures. This is followed by hippocampal and other limbic lesions. The electrographic and lesioning are not unlike those in TLE. There is a preference for CA1 and CA3 regions, GABAergic interneurons, pyriform cortex, and other limbic regions. (Ben-Ari, 2008)

³⁰²³ A group of lipid storage disorders, e.g. Gaucher's disease.

³⁰²⁴ An example of a myoclonic disorder that is not associated with seizures is *paramyoclonus multiplex*. The patient is usually an adolescent with widespread muscle jerks.

³⁰²⁵ **Unverricht-Lundborg disease (Baltic or Mediterranean myoclonic epilepsy)**, an autosomal recessive disorder commencing between 6 and 18 years of age, involves stimulus sensitive myoclonus, generalised seizures, ataxia, dysarthria, intention tremor, and dementia. Most cases are due to an unstable expansion of a dodecamer repeat in the 5' region of the cystatin B gene on 21q22.3. A few cases are due to point mutations at the same site. Cystatin B is important in maintaining the structure of nerve cells.

³⁰²⁶ **Benign familial neonatal convulsions (BFNC)** is an autosomal dominant disorder starting anywhere in the first 4 months after birth. Unprovoked generalised or multi-focal seizures of tonic and/or clonic type are seen. There may be breathlessness, eye symptoms, or other indicators of autonomic involvement. Most patients remit by 6 months of age. A minority re-occur during the school years or in young adulthood when seizures may be proved (e.g. by lack of sleep).

BFNC must be distinguished from **benign familial infantile convulsions** (autosomal dominant early childhood partial epilepsy, onset 4-6 months with remission before 3 years; mutations on different chromosomes in different families) and **benign familial neonatal/infantile convulsions** (same family may have onset in neonatal period or early infancy; mutations in voltage-gated sodium channel subunit SCN2A).

³⁰²⁷ Brief loss of muscle tone with falls +/- loss of consciousness.

bilateral temporal but often widespread abnormalities. There are almost continuous spike and wave discharges during slow wave sleep. Most develop seizures around the time that the language changes occur. Onset may be acute or subacute. Two-thirds are left with a receptive language deficit, but the remainder recover completely. Early diagnosis and speech training are important. Remedial or special schooling may be required. Multiple subpial resections may be employed in treatment.

Acquired epileptic opercular syndrome

This is a variant of Landau-Kleffner syndrome. There is progressive loss of voluntary movement of the mouth. The patient has problems with oral expressive movements such as kissing. Feeding difficulties and drooling may also be present. The EEG shows almost continuous spike and wave discharges bilaterally in the rolandic areas during slow wave sleep.

EEG in epilepsy

<i>Appropriate history</i>	<i>Abnormal EEG</i>	<i>Is there epilepsy?</i>
Present*	absent	probably
Absent	present	no
Absent	absent	no
Present	present	yes

*Epilepsy is most likely present if there is a collateral history, if you can see the event, if there is a suggestive cause like tumour or epiloia, if there are signs like scars/bitten tongue/incontinence, if there is a family history (40% of idiopathic generalised cases), etc. You must outrule pseudoseizures, syncope, etc.

10% of normals have epileptiform EEG activity but no history of seizures. Half of epileptic patients have normal routine EEG. After 4 spaced routine EEGs there is a 92% chance of detecting an abnormality. Nasopharyngeal leads carry placement problems, discomfort and frequent artefact. Sphenoidal EEG (via cheeks into sphenopalatine fossae) is used preoperatively.

Syncope (fainting) follows a temporary reduction in cerebral blood supply. Aura (epigastric sensation, vertigo, visual and somatosensory phenomena) is common. There may be myoclonic jerks³⁰²⁸, deviation of the eyes, flickering of eyelids³⁰²⁹, and vocalisation that may confound the unwary diagnostician. Prolactin levels may be raised with syncope.

Stages of tonic-clonic seizures³⁰³⁰

Prodrome – hours/days – uneasiness/irritability/headaches/appetite change

Aura – seconds/minutes – e.g. epigastric sensation (*Déjà vu* may indicate right temporal focus – Plamini & Gloor, 1992)

Tonic – 10-30 seconds – arms flexed and adducted, legs extended, air expelled as a cry, cyanosis, & unconscious

Clonic – 1-5 minutes – violent muscular jerking, bitten tongue, incontinent

Postictal – minutes/hours – unconscious, flaccid, extensor plantar responses, no corneal reflex, headache, confused, muscle aches, +/- automatic or violent behaviour

International Classification of epileptic seizures (simplified)

FOCAL/PARTIAL/LOCAL

With motor symptoms (with [Jacksonian] or without *march* [spread], versive, postural, phonatory [with sounds or arrest of speech]), with somatosensory or special sensory symptoms (somatosensory³⁰³¹, visual³⁰³², auditory³⁰³³, olfactory, gustatory, vertiginous), with autonomic symptoms/signs, with psychic symptoms (e.g. dysphasia, fear, macropsia, musical hallucinations, thought crowding³⁰³⁴, forced thinking³⁰³⁵).

COMPLEX FOCAL

Depending on whether impaired consciousness is present at the start or develops later in the course of the seizure, and whether there is secondary generalisation.

GENERALISED

Absence, atypical absence, myoclonic, clonic, tonic, tonic-clonic, atonic.

International classification of epilepsies and epileptic syndromes

³⁰²⁸ Usually these consist of minor twitches and must be distinguished from tonic-clonic seizures.

³⁰²⁹ *Eyelid myoclonia* with absences (jerking eyelids, eyes may jerk upwards, and the head may be pushed backwards) is a manifestation of an idiopathic generalised epileptic syndrome as is *perioral myoclonia* (absences with jerking of perioral and masticatory muscles).

³⁰³⁰ Generalised tonic-clonic seizures may have autonomic manifestations, e.g. pupillary athetosis (**hippus**), i.e. rhythmic contraction and dilation of the pupils. Less commonly there may be mydriasis or miosis.

³⁰³¹ Partial sensory seizures arise in sensory cortex. Unpleasant contralateral face/limb sensations (tingling/electric) experienced - can spread in Jacksonian-like manner in a seconds (much faster than focal sensory episodes in migraine).

³⁰³² Discharges from the occipital area cause flickering lights and flashes of red or white that must be differentiated from the zig-zag of migraine.

³⁰³³ Auditory seizure phenomena (hissing, roaring, buzzing) are due to discharge from Heschl's convolution (anterior transverse temporal gyrus) and superior temporal convolution.

³⁰³⁴ A feeling of disorganised thoughts being hurried along.

³⁰³⁵ A subjective compulsion to dwell on a certain word or topic.

LOCALISATION-RELATED (FOCAL, LOCAL, PARTIAL), e.g. primary reading epilepsy.

SYMPTOMATIC, e.g. temporal lobe epilepsy

GENERALISED EPILEPSIES & SYNDROMES – idiopathic (age-related such as benign neonatal convulsions, childhood absence epilepsy [pyknolepsy], etc), cryptogenic (= cause suspected) or symptomatic (e.g. Lennox-Gastaut syndrome), symptomatic (of a known disorder).

UNDETERMINED AS TO BEING FOCAL OR GENERALISED, e.g. Landau-Kleffner syndrome.

Causes of death in epilepsy

Unrelated

Seizures

Unexplained sudden death

Drowning³⁰³⁶

Other accidents

Suicide (c. 9%)³⁰³⁷

Underlying cause of epilepsy (e.g. tumour, CVA, degenerative illness)

Status epilepticus (7-39% short-term)

Unknown

The epilepsy population has a standardised mortality ratio (SMR) of 2-3, the idiopathic group having only a slightly increased rate whereas cases arising from known causes account for most of the increased mortality. Population-based studies suggest that mortality is related more often to underlying aetiology rather than the seizures. (Tomson & Forsgren, 2005)

Prolactin: The serum prolactin rises to 1,000 munits/L 20 minutes after most, but not all, generalised seizures³⁰³⁸ (returning to baseline after 6 hours) and is unchanged or moderately raised following pseudoseizures and complex partial seizures. There may be no rise after serial seizures or following status epilepticus. Syncope may raise prolactin levels. Pseudoseizures may be associated with modest elevations of prolactin.

White cell count (WCC): The WCC may increase transiently after a seizure (noradrenaline release and demargination of white cells), but there is no associated 'left shift' as might occur with infection.

Cardiac investigations: Ambulatory ECG for dysrhythmias, echocardiography (structural problems) and tests for changes in blood pressure on standing.

Prognosis: Factors associated with a poor prognosis are a high frequency of tonic-clonic seizures before treatment, partial seizures, neurological deficit, psychiatric and social problems (stress, low socioeconomic status and poor educational attainment), a family history of epilepsy, and a poor response to treatment. (Shorvon, 1991; Betts, 1992; Callaghan ea, 1992) Good outcome is associated with benign epilepsies³⁰³⁹, generalised absence seizures, provoked seizures, long remissions, and recent onset. Onset of idiopathic seizures before age 15 years have shown a cumulative risk of recurrence of 40% at 2 years, and EEG abnormalities increase the seizure recurrence risk. Drug-resistant epilepsy may be more common when seizures are not arrested early on by treatment. (Reynolds, 1990) Data from life insurance statistics suggest a standardised mortality ratio about 2.5 times that of a non-epileptic population.

Febrile seizures: One definition of a febrile convulsion is a seizure associated with fever in infancy or childhood without evidence of intracranial infection or a defined cause other than infection outside the CNS. It is the most common type of seizure. About one child in 30 has at least one febrile convulsion between the ages of 6 months and 6 years, especially between 2 and 4 years. Death is rare. (Vestergaard ea, 2008)

Recurrences of febrile seizures

³⁰³⁶ E.g. during unsupervised bathing.

³⁰³⁷ Risk factors include past psychiatric history, past suicide attempts, and early onset of epilepsy (especially in adolescence). The FDA issued warnings in 2008 that antiepileptic drugs may increase suicidal thinking and behaviour but Gibbons ea (2009) found the opposite in bipolar patients taking this class of medicines!

³⁰³⁸ The prolactin level should be measured 20 minutes after a seizure (post-ictal level) and then compared with the level found in blood at least 6 hours following a seizure or taken at the same time of day when there is no seizure (baseline level).

³⁰³⁹ E.g. benign Rolandic epilepsy.

Occur in one-third of cases

Associated with low risk for epilepsy: 2-4%

Associated with recurrence - fever lasts only a brief time before the fit; temperature not too high before the seizure; complex features of first attack; neurodevelopmental disorders; child < 18 months old; a family history of febrile convulsions; family history of epilepsy; complex febrile seizures (different sources disagree on some of these risk factors, due in part to differences in definition)

About 2.4% of those children who were previously normal will go on to develop at least two non-febrile seizures, i.e. epilepsy. Individual fits respond to rectal diazepam administered by parents. Sadleir and Scheffer (2007) suggest buccal or intranasal midazolam for the 9% of cases with prolonged febrile seizures. Longterm prophylaxis was probably overused in the past. In fact, in the small number of cases who do develop epilepsy the causative role of febrile seizures is tenuous. Phenobarbitone (phenobarbital) treatment is associated with lower IQ scores that persist for many months after the drug is stopped. (Farwell et al, 1990) Carers and/or family require education and reassurance.

Rarely one sees families who seem to have an autosomal dominant inheritance. In some cases febrile seizures persist after age 6 years, plus or minus afebrile seizures (*generalised epilepsy with febrile seizures plus*).

Absence (petit mal) seizures (3 Hz spike-and-wave EEG activity) are seen especially in children and have a tendency to remit over time. By adult life up to 4 out of 5 cases will have remitted. Also, as time passes, the attacks become shorter and more infrequent. Absence attacks very often convert to generalised tonic-clonic attacks: 40% after 5-10 years convert. Absence seizures are thought to be due to abnormal thalamocortical circuitry. There is a strong genetic predisposition. Hyperventilation precipitates attacks.

Autopsy: Denning and Berrios (1994) described 38 males and 18 women with autopsy from the literature. 59% had a neurological disorder, most frequently epilepsy. Right- and left-sided lesions were equally represented. Psychotic disorder was also present in 59%, e.g. delirium or depressive.

Temporal lobe epilepsy (TLE) is common³⁰⁴⁰. All limbic structures have a low seizure threshold. The pathology varies from study to study but ischaemia at birth seems important³⁰⁴¹. The anterior temporal and the frontal lobes are highly susceptible to damage from head injury³⁰⁴², and contracoup lesions are commonest at these sites. MRI may reveal loss of hippocampal volume or symmetry. Functions attributed to the limbic structures are many. It therefore is no surprise that the aura may take many forms, such as smells (usually noxious), sorrow, apprehensiveness, elation, visceral sensations, vertigo, tunnel vision (concentric constriction of visual field), or there may be no aura. Déjà vu, jamais vu, grimacing, smacking of lips, depersonalisation, derealisation and aggressiveness may all characterise a seizure. The patient may experience suspiciousness, extreme fear or rage as part of the ictus. Aggressive outbursts may also occur between attacks. Alternatively the patient may become confused and, for a brief while, carry out some semi-purposive action. Disturbed behaviour may occur in a state of clouded consciousness (psychomotor or complex partial status/fugue/twilight state/furor) and this may persist for hours, days, or even weeks. Neuroleptics may be required. The attack may stop of its own accord, or it may be terminated by a grand mal seizure or by a single electroshock (ECT). The author has seen a couple of patients with TLE who believed that one of their eyes contained an evil spirit and who made repeated attempts to pluck the eye out.

Features of complex partial seizures:

Autonomic and visceral ('epigastric aura', dizziness, flushing, tachycardia, other bodily sensations)

Perceptual (distorted perceptions, déjà vu, and olfactory, somatic, visual, auditory hallucinations)

Cognitive (disturbed speech, thought and memory)

Affective (fear and anxiety)

Psychomotor (automatisms, grimacing and other bodily movements, repetitive or more complex stereotyped behavior, changes in breathing, autonomic symptoms)

³⁰⁴⁰ Fyodor Dostoyevsky (1821-1881), Russian writer (*The Brothers Karamazov* and *Crime and Punishment*) and philosopher, had epilepsy (first seizure at age 9 years), perhaps TLE. This may have inspired him to create characters with epilepsy, e.g. Prince Myshkin in *The Idiot*.

³⁰⁴¹ Chromosomal abnormalities (4q) occur in some families with mesial TLE. (Hedera et al, 2007)

³⁰⁴² As illustrated by the research on monkeys conducted by R H Pudenz and C H Sheldon during the 1940s.

The focus in the cases of psychomotor seizures is usually in the temporal lobe and sometimes in the inferior frontal lobe³⁰⁴³.

Complex partial status is associated with confusion, psychosis, fluctuating consciousness, automatisms, episodic hallucinations, marked mood changes, and a diagnostic EEG. IV diazepam is given early because prolonged status may cause persistent intellectual deficits.

Amnesic seizures are characterised by amnesia³⁰⁴⁴ with no other features. The patient is able to carry on normally during the ictus but cannot remember what they did during this time.(Palmini ea, 1992) Onset is in early adulthood. Other seizure types, such as complex partial seizures, can be recognised from the history.

Epilepsy and schizophrenia-like psychosis (ESLP): The connection between ‘schizophrenia’ and epilepsy are possibly more tenuous than when Slater studied this phenomenon.(Slater ea, 1963) Negative studies suggest that sampling bias (e.g. using clinic cases) may have led to a spurious connection. Methodological issues, such as use of discharge diagnosis rather than research diagnosis, hinder interpretation of positive studies. Nevertheless, depth recording of patients awaiting temporal lobectomy has supported the notion that left (see box) temporal foci might carry a special risk for schizophrenia. In a study involving MRI and MRS (Maier ea, 2000) spectroscopic abnormalities were more pronounced in the epilepsy groups (TLE only and TLE + psychosis) and were bilateral, and abnormalities in a group with a diagnosis of schizophrenia only were left-sided. Specific regional hippocampal/amygdala volume reductions were most marked in the group with TLE + psychosis and were bilateral. Left-sided regional volume reductions identified in the dominant hemisphere of schizophrenic patients were also present in the TLE + psychosis group, but not in TLE-only patients. Perhaps this region in the left temporal lobe plays a major part in the genesis of psychosis.

Problems with conclusions about left-sided foci (Sachdev, 2007, p. 275)

Some negative laterality studies

Varied rigour when establishing laterality (e.g. are surface electrodes adequate?)

A one-sided focus does not prove that the other side is normal

Left-sided foci may just be more common for temporal lobe epilepsy

ESLP may have generalised seizures plus a temporal focus

Diagnosis of psychosis is very language dependent, biasing left-sided lesions

Lack of neuropathological support for predominance of left-sided lesions

*Forced normalisation*³⁰⁴⁵ is the situation where the EEG becomes more normal in an epileptic who then develops a paranoid, manic or schizophrenia-like psychosis (*alternative psychoses*), depressed, anxious, dissociated, or simply becomes behaviourally disturbed. The author has had good results with a single application of ECT in such cases. One theory is that chronic temporal ictal lesions cause kindling of activity in other brain areas, especially forebrain limbic areas, with the gradual development of psychosis. Over-controlled epilepsy (by drugs or vagus nerve stimulation: Gatzonis ea, 2000) should lead to a reduction of anticonvulsant doses. Dolmatil has been suggested for epileptic psychosis. A regime that allows the odd seizure and a clear sensorium is superior to complete control at the expense of cognitive impairment.

Temporal lobectomy may be a risk factor for schizophrenia-like psychosis.(Sachdev, 1998)

³⁰⁴³ If the focus is the frontal lobe, seizures often occur in clusters, the start and end of the seizure are often sudden, there is little in the way of confusion later, and content is often bizarre: subject might act as if riding a bicycle or having sexual intercourse, or may emit sounds.

³⁰⁴⁴ Mostly anterograde, sometimes combined anterograde-retrograde, and rarely retrograde. Kapur (1990, pp. 140-151) described *transient epileptic amnesia*: episodes of amnesia, usually occurring in an older person whilst waking, lasting up to an hour and sleep EEG may be necessary to reveal epileptic origin; whilst amnesia may be the only ictal manifestations other TLE phenomena may occur.

³⁰⁴⁵ Described by Heinrich Landolt (1917-1971) of Switzerland in 1953, *forcierte Normalisierung*, paradoxical or spurious normalisation, this phenomenon was inspired by seeing patients who’s EEGs improved as their behaviour worsened. Not all short-lived inter ictal psychoses show forced normalisation and some cases of post-ictal psychosis show forced normalisation.(Sachdev, 2007, p. 270)

In general, schizophrenia-like psychosis associated with cerebral trauma is more likely if there is a genetic predisposition to schizophrenia or if there is severe injury with significant brain damage and cognitive impairment.

Findings of Qin et al (2005)

- Increased incidence of schizophrenia and schizophrenia-like psychosis in people with history of epilepsy
- Family history of psychosis or epilepsy is a risk factor for schizophrenia and schizophrenia-like psychosis
- Effect of epilepsy greatest if there is no family history of psychosis
- The increased risk for schizophrenia and schizophrenia-like psychosis does not differ by type of epilepsy but is increased with a greater number of hospital admissions and is greater for those who are first admitted for epilepsy at later ages

Findings of Adams et al (2008):

- 319 cases of focal epilepsy admitted for video EEG monitoring
- Significant association found between prevalence of depressive symptoms and non-lesional focal epilepsy
- No significant differences in prevalence of neuropsychiatric disorders between epilepsy arising in temporal lobe or outside it

Geschwind syndrome (Benson, 1991) is a somewhat controversial interictal syndrome said to be found in some longstanding cases of TLE. The patient experiences certainty, the 'truth' ('eureka' feeling), clairvoyance, mystical or cosmic consciousness, all of which may seem to 'float', i.e. the patient is unable to link the experience to a specific content.

Epileptic automatism may be defined as a state of clouding of consciousness which occurs during or immediately after a seizure and during which the individual retains control of posture and muscle tone and performs simple or complex movements and actions (e.g. undressing) without being aware of what is happening. It is rarely a justifiable defence for crime. Automatism is legally defined as an unconscious involuntary action and two types are recognised: 'insane' (absent *mens rea* - caused by disease of the mind - insanity verdict with compulsory detention in hospital) and 'non-insane' (mind affected by some external factor - complete acquittal). From the medical standpoint this approach is naïve and the court should have discretionary powers of disposal in individual cases.

Most cases of violence in association with epilepsy occur when attempts are made to restrain a patient who is experiencing a seizure.³⁰⁴⁶

Interictal depression is common. Rates of depression, often atypical and dysthymic with brief intervals of euthymia, and suicide are about 4 to 5 times those found in the population at large, and suicide may be 25 times the general population rate in people with TLE. (Harris & Barraclough, 1997) Some depressive feeling are found in the majority of epileptics. The combination of interictal dysthymia and intermittent irritability, impulsiveness, anxiety and somatic symptoms has been called interictal dysphoric disorder by Blumer et al. (1995) Brain and brainstem changes in 5-HT_{1A} receptor density have been reported in major depressive disorder and in TLE using PET and Lothe et al (2008) used PET to confirm changes in central serotonergic pathways³⁰⁴⁷ (probably decreased extracellular serotonin concentration but possibly receptor upregulation) in depressed TLE patients.

Interictal panic disorder affects about one-fifth of epileptics. (Pariente et al, 1991)

Anticonvulsants (AEDs)

A small number of patients treated with AEDs may experience thoughts of self harm or suicide and patients should be monitored for these and for depression. (Irish Medicines Board, 2009)

³⁰⁴⁶ An association between **violence and epilepsy** is more likely under the following circumstances: the person has proven epilepsy, there is no obvious external gain/motive, he was obviously having a seizure when he was violent and the stereotyped seizure pattern for that individual is consistent with the reported behaviour, and the behaviour/thinking is not structured/deliberate/conscious as when the patient goes to another part of the house to collect a dangerous weapon where he knows it to be stored.

³⁰⁴⁷ Especially found in raphe nuclei, insula, cingulate gyrus, and epileptic hippocampus.

General rules include avoiding high levels and polypharmacy, monitoring behaviour and school performance, and avoiding barbiturates in children where possible. When changing from one drug to another: add second drug slowly to full dosage and only then withdraw first drug slowly. Monotherapy should be tried for six months for epilepsy, before any changes in medication are made. Carbamazepine is a commonly used drug, phenytoin being less often employed than heretofore. Sodium valproate has teratogenic effects in women during their childbearing years. Any young woman free from fits for 2 years should be offered the choice of withdrawing from anticonvulsant treatment. Proposed mechanisms for mental effects of anticonvulsants include neuropathological damage, folate deficiency, effects on monoamine metabolism, and effects on hormone metabolism. Anticonvulsant-induced encephalopathy (e.g. phenytoin or valproate) may produce a (reversible) dementia-like picture, +/- focal signs and dyskinesias, in association with increased CSF protein levels. Consider this diagnosis in an epileptic who develops cognitive impairment³⁰⁴⁸.

Most AEDs work by enhancing GABA neurotransmission. Antiepileptic drugs (AEDs) promote metabolism of the contraceptive pill. Therefore a different form of contraception may be required. ECT is rendered less effective if the seizure duration is shortened with Lidocaine. Certain anticonvulsants, such as phenobarbitone (phenobarbital), may cause depression. Toxic levels may cause 'sticky' (slow) cerebration and movement. Ataxia is then likely. However, phenobarbital³⁰⁴⁹ is cheap and may be affordable in non-affluent societies. (Kale & Perucca, 2004) Frequent fitting and recurrent head trauma may lead to coarsening of the personality. Drugs may be stopped as a form of protest against having the condition. Folate deficiency may be due especially to phenytoin (Epanutin) but over-treatment with folic acid may cause dyscontrol because of its own effects on plasma anticonvulsant levels. Reduced sex drive in treated epileptics may in part be due to increased destruction of sex hormones by induced liver enzymes.

Anticonvulsant and other drugs

Carbamazepine (Tegretol; O'Shea, 2002b) is an iminodibenzyl related to imipramine. It can also be classified as a carboxamide. Carbamazepine suppresses repetitive neuronal firing by stabilising voltage-gated sodium channels. It is indicated for generalised tonic-clonic seizures, partial seizures, paroxysmal pain (e.g. trigeminal neuralgia), alcohol withdrawal, BZD withdrawal, mania, and prophylaxis of bipolar affective disorder and perhaps unipolar melancholic depression. It may exacerbate petit mal (absence) seizures. Carbamazepine should be avoided in those patients who have AV conduction defects³⁰⁵⁰ or porphyria. It should be stopped if there is an allergic skin reaction or deterioration in liver function. Routine liver function tests may be performed more often for legal reasons rather than for cost-effectiveness and some experts suggest that hepatotoxicity, a rare phenomenon with anticonvulsants, may be picked up more readily by clinical examination than by laboratory examination. White cell counts and LFTs should be performed at baseline and, perhaps, at intervals thereafter. However, has been argued that routine WCC counts will miss agranulocytosis because of its rarity and sudden onset. It may be safer to ask patients to report pyrexia, pharyngitis, other infection, petechiae, or weakness and pallor. Non-progressive or fluctuating leucopaenia (and anaemia), often early in treatment, is common and usually harmless. Should the leucopaenia be severe or accompanied by clinical signs (e.g. pyrexia or sore throat) the drug should be stopped and the WCC checked. Serious side effects, such as agranulocytosis and aplastic anaemia, occur in only 1 in 10,000 to 120,000 treated patients³⁰⁵¹. It may be necessary to cover sudden withdrawal with a BZD. Carbamazepine may interfere with driving and it can cause folate deficiency. The half-life of

³⁰⁴⁸ There are many causes of **cognitive dysfunction** in association with epilepsy: primary brain dysfunction, brain damage caused by seizures including status, head injury, medication, other drugs including alcohol, and the psychosocial difficulties that may accompany the disorder. Between 10-20% of epileptic children have persistent or progressive intellectual impairment, especially when seizures are poorly controlled and when there are adverse psychosocial circumstances. Perhaps as a result of atrophy of the hippocampus as a result of seizure activity, deterioration of memory function is common in adults whose TLE is poorly treated.

³⁰⁴⁹ Drug-induced falls in **testosterone levels** may cause sexual problems in either sex. Anticonvulsant drugs, by inducing liver enzymes, may increase circulating levels of sex hormone-binding globulin with consequent reduction in levels of unbound testosterone. Phenobarbital, phenytoin and carbamazepine are particularly likely to do this, but lamotrigine is unlikely to do so.

³⁰⁵⁰ Anything greater than first degree heart block.

³⁰⁵¹ Some authors put it at 1 in >575,000 treated patients/year.

carbamazepine is 13-17 hours and there is 70-80% protein binding. Drugs such as cimetidine, dextropropoxyphene, diltiazem, erythromycin, INAH, viloxazine³⁰⁵², and verapamil inhibit the metabolism of carbamazepine. Nifedipine does not have this effect. Fluoxetine may increase carbamazepine levels. Valproate raises the concentration of the toxic 10,11-epoxide metabolite of carbamazepine so that while carbamazepine levels may be normal the patient may be toxic since the metabolite is not being measured. Carbamazepine induces liver enzymes and can reduce the effectiveness of some drugs, e.g. antipsychotics, steroids (including oestrogen), theophylline, warfarin, and other antiepileptic drugs. TCA plasma levels may be reduced by 40-45% for the same reason. The dosage of anticoagulant drugs may require modification. Contraceptive drugs may show reduced efficacy and there may be breakthrough bleeding or spotting; it is recommended that a pill containing at least 50 mcg of oestrogen is used or that another method of contraception is employed. Strictly, carbamazepine should be avoided within two weeks of MAOI therapy to avoid hypertensive crisis, but the combination has been safely employed. Side effects of carbamazepine are usually most marked early in treatment.

Carbamazepine: side effects

CNS – dizziness, diplopia, blurred vision, headache, somnolence, ataxia, confusion (with agitation in elderly), dystonia, worsening of multiple sclerosis symptoms
 GIT – dry mouth, nausea, diarrhoea, constipation, anorexia
 Metabolic – water intoxication, hyponatraemia
 Endocrine – low T4 level with normal TSH level³⁰⁵³
 Skin – reversible generalised erythema in c 3%, and (rarely) severe reactions like exfoliative dermatitis, Stevens-Johnson syndrome (rash with symptoms equivalent to a severe burn – may kill from superimposed bacterial infection or lead to disfigurement), toxic epidermal necrolysis, hair loss
 Haematology – leucopaenia (may be reversed by lithium), thrombocytopenia, agranulocytosis, aplastic anaemia, thromboembolism
 Others – oedema (dose-dependent), fever, proteinuria, lymphadenopathy, acute renal failure, cardiac conduction disorders³⁰⁵⁴, hepatitis³⁰⁵⁵, immunoglobulin deficiency
 Overdose³⁰⁵⁶ – tremor, excitement, seizures, hypo- or hypertension, diminished consciousness, EEG and ECG (including arrhythmias) changes

*Oxcarbazepine*³⁰⁵⁷ (Trileptal – 150 mg, 300 mg, and 600 mg tablets and 60 mg/ml oral suspension): This 10-keto analogue of carbamazepine is used for partial seizures with/without generalised tonic-clonic seizures, as mono- or adjunctive therapy. (Anonymous, 2002c) It may offer improved tolerability over carbamazepine and there is disputed evidence that it might be efficacious in bipolar disorder (Hirschfeld & Kasper, 2004; Grunze, 2008) Dose is adjusted in elderly or with poor renal function or risk of *hyponatraemia*. Dosage adjustment not needed for mild/moderate hepatic impairment. Monitor serum sodium for hyponatraemia (2.5% incidence – severe cases can lead to seizures). Weigh regularly (to detect fluid retention) if there is cardiac insufficiency/failure. Very rarely causes hepatitis, usually with good outcome. May render anovulants ineffective (may need higher potency contraceptive or supplementation with barrier method). Inhibits CYP2C19 and therefore can affect phenobarbitone (phenobarbital), phenytoin, etc. Can induce CYP3A4 and 3A5 so increasing metabolism of dihydropyridine calcium antagonists, anovulant pills, and anticonvulsants such as carbamazepine. It does not reduce the anticoagulant effect of warfarin. No autoinduction has been noted. Avoid with MAOIs on theoretical

³⁰⁵² Withdrawn from market.

³⁰⁵³ Clinical hypothyroidism is unusual and may be due to reduced TSH response to TRH. Whilst lithium causes a decreased thyroxine with increased TSH, carbamazepine causes a decrease in thyroxine with normal TSH.

³⁰⁵⁴ Quinidine-like action of this tricyclic drug: consider valproate for patients with heart disease who have bipolar affective disorder.

³⁰⁵⁵ Less than 5% of patients experience a benign rise in liver enzyme levels and perhaps less than 1 in 10,000 patients experience a serious acute hepatic necrosis and then usually during the first weeks of therapy.

³⁰⁵⁶ Following massive overdose, peak plasma concentrations may be reached on second or third day after ingestion.

³⁰⁵⁷ This is the 10-keto analogue of carbamazepine. Liscarbazepine is an active metabolite of oxcarbazepine which has been tried for mania with little success. Eslicarbazepine, an isomer of liscarbazepine, is being studied as a possible mood stabiliser.

grounds because it is a TCA relative. There is a possibility of neurotoxicity if it is combined with lithium. Avoid breastfeeding (milk-plasma ratio = 0.5) and possible teratogenicity (cleft palate?). Common problems: fatigue, asthenia, dizziness, headache, somnolence, agitation, apathy, amnesia, ataxia, impaired concentration, confusion, depression, nervousness, nystagmus, tremor, nausea, vomiting, constipation, diarrhoea, abdominal pain, hyponatraemia (esp. in elderly), acne, alopecia, diplopia, vertigo. Uncommon: leucopaenia, increased transaminases +/- alkaline phosphatase, urticaria. Rare: angioedema, rash (Stevens Johnson, SLE), fever, lymphadenopathy, abnormal LFTs, eosinophilia, thrombocytopaenia, arthralgia, cardiac arrhythmia (A-V bloc, etc), hepatitis, hyponatraemic seizures, confusion, encephalopathy. Between 25-31% of patients with allergy to either oxcarbazepine or carbamazepine are allergic to both drugs. Oxcarbazepine's metabolite MHD³⁰⁵⁸ blocks voltage-sensitive sodium channels. Elimination of metabolites is mainly renal.

Sulthiame (Ospolot): Sulthiame, an anti-epileptic sulphonamide like acetazolamide, may increase phenytoin levels into the toxic range.

Barbiturates: These can cause hyperactivity, attention deficit disorders, behavior disorder, and cognitive deficits. Phenobarbital raises the seizure threshold probably by membrane stabilisation.

Primidone (Mysoline): Converted to phenobarbitone by liver. It has been associated with psychosis and depression.

Phenytoin (Epanutin): May act by limiting the spread of discharge, probably by membrane stabilisation. Can be given once daily because plasma half-life = 24-36 hrs. There may be facial coarsening, gingival hyperplasia, acne and hirsutism. Osteomalacia may occur due to reduced calcium absorption. Chronic encephalopathy can occur with high therapeutic levels, and acute delirium (especially in the elderly) is also described. Abnormal cognition can occur with low folate levels. There have been some cases of fatal acute liver disease, usually when given with other anticonvulsants. It is best avoided in presence of active liver disease. Sulphonamides decrease phenytoin metabolism and may precipitate phenytoin toxicity.

Valproate: A short chain fatty acid³⁰⁵⁹ that is useful for generalised epilepsy. (Marson ea, 2007a) Chronic encephalopathy can occur with high levels. Weight gain can occur. Thrombocytopaenia is a relatively frequent side effect of valproate in the elderly. (Trannel ea, 2001) Beta-blockers reduce tremor caused by either lithium or valproate. Aspirin increases valproic acid levels.

Ethosuximide: This succinimide may be associated with psychosis, especially in young adolescents.

Benzodiazepines: BZDs, valproate, barbiturates and vigabatrin may work by enhancing the effects of GABA. Diazepam can be given by rectal infusion for status epilepticus. Intravenous lorazepam may provide a more prolonged anticonvulsant effect than is achieved with intravenous diazepam. (Leppik ea, 1983) (ECT may also be used to treat status: Petrides ea, 2004) Clonazepam's effects are reduced after a few weeks. There may be increased aggressiveness or children may become irritable and hyperactive. Clobazam (Frisium) is often better tolerated than clonazepam but it has the same problem of tolerance, but it may be of use for special occasions, catamenial seizures, or for seizures occurring in clusters.

Drug treatment protocol for convulsive status epilepticus³⁰⁶⁰ (abbreviated from Renganathan ea, 2007; Mellers, 2009, p. 375)

Lorazepam 4 mg IV bolus repeated if needed after 10 minutes

OR

Diazepam 5-10 mg over 1-2 minutes repeated at 15 minute intervals if needed (max: 20 mg)

OR

Midazolam 10 mg by buccal route given by carer or ambulance personnel, repeatable 15 minutes later

IF SEIZURES CONTINUE:

Inform anaesthetist

Phenytoin 15-18 mg/kg IV not faster than 50 mg/minute (half this for elderly) – then 5-6 mg/kg bolus every 6 hours

OR

Phenobarbitone 10 mg/kg (not faster than 100 mg/minute) – then 1-4 mg/kg/day PO, IV or IM

IF SEIZURES CONTINUE:

³⁰⁵⁸ Formed by hepatic cytosolic enzymes.

³⁰⁵⁹ Valproate, tiagabine and vigabatrin are fatty acids.

³⁰⁶⁰ **Status epilepticus** = epileptic activity persisting for at least half an hour. If the seizure is tonic-clonic it is called convulsive status. Status affects 1 in 20 adults during life, but the figure for children is one-quarter. Treatment is needed when at least 5 minutes elapses. Absence status, although benign, may be stopped with benzodiazepines. The same applies to complex partial status. (Mellers, 2009, p. 375)

Involve anaesthetist
 ICU, intubation, cardiorespiratory support
Thiopentone 100-250 mg bolus over 20 seconds – then 50 mg bolus every 2-3 minutes until seizures stop – may require follow-on infusion

Lamotrigine (Lamictal, Lamotrigine Ranbaxy): Useful for partial (Marson *et al*, 2007b) and generalised tonic-clonic seizures that are not satisfactorily controlled by other AEDs. Lamotrigine inhibits excitatory presynaptic neurotransmitter release, especially glutamate. It also blocks sodium channels and 5-HT₃ receptors. Does not induce or inhibit hepatic drug-metabolising enzymes. A limited number of reports of breakthrough seizures, unexpected pregnancies and of menstrual bleeding disorders (such as breakthrough bleeding) have been reported to GlaxoSmithKline in women on a combination of lamotrigine and the contraceptive pill. Anovulants decrease serum levels of lamotrigine and such levels may rise on stopping the contraceptive pill. Lamotrigine increase sense of well being. Some patients report an improvement in sexual interest (unlike other AEDs). Rare associated problems are severe allergic skin rash (Stevens Johnson or toxic epidermal necrolysis/Lyell syndrome) and psychiatric (sometimes aggressive) reactions. Drugs that induce liver enzymes like carbamazepine or phenytoin can halve the half-life of lamotrigine, while sodium valproate, which inhibits its metabolism, can double the half-life of lamotrigine. Lamotrigine may precipitate carbamazepine toxicity. Side effects include rashes, headache, nausea and vomiting, dizziness, diplopia, ataxia, and, in high doses, tremor. Leucopaenia and thrombocytopenia can occur. Hypothyroidism is a rare complication. Lamotrigine has been reported to cause a condition resembling Tourette's syndrome in children that is reversible on stopping the drug. (Kellett & Chadwick, 2004, p. 331) Avoid lamotrigine during pregnancy or lactation.

Vigabatrin (Sabril): A GABA analogue (one of the gamma-amino acids) that irreversibly inhibits the enzyme responsible for GABA catabolism (GABA transaminase) thereby increasing GABA availability in the synaptic space. Vigabatrin has been suggested as an add-on treatment for partial seizures, with/without secondary generalisation, uncontrolled by other drugs or monotherapy for infantile spasms. In practice, its use is restricted because of ophthalmic problems to very severe epilepsy (e.g. West syndrome). Finnish research originally raised concerns about risk of inducing dystonia, dyskinesia, and hypertonicity as well as 'cytotoxic oedema' on MRI. The latter appear to be more likely in babies receiving doses of at least 125 mg/kg/day. However, these MRI changes were asymptomatic and transient and usually resolved whether vigabatrin was continued or not. (Wheless *et al*, 2009) Vigabatrin therapy should only be initiated by epileptologists, neurologists or paediatric neurologists. It can cause drowsiness, fatigue, nervous irritability, aggression and psychosis (especially if there is a history), depression, disturbed vision (*irreversible visual field defects in one-third of cases – may take months or years to develop*) and memory, excitement and agitation in children, and increased frequency of (especially myoclonic) seizures. All patients should be screened at the start of treatment and regularly thereafter for visual field defects. Dose reduction is indicated for significant renal impairment. Dose may need adjustment because of combination with other agents. Avoid during pregnancy or lactation. Interestingly, vigabatrin may have utility in treating cocaine dependence. (Brodie *et al*, 2009) A risk-benefit analysis should be conducted before prescribing vigabatrin. According to Clarke (2009, p. 1142) vigabatrin 'is no longer advocated' because of the effects on vision. *Lacosamide* (Vimpat) is an adjunctive treatment for partial-onset seizures with/without secondary generalisation in epileptic patients aged at least 16 years. It modulates sodium channel activity in a novel way. It binds to collapsin response mediator protein-2 (CRMP-2³⁰⁶¹). It may be associated with depression, headache, somnolence, asthenia/fatigue, dizziness/vertigo, problems with balance/gait (may fall), pruritus, nausea/vomiting/constipation/flatulence, tremor, nystagmus, double and blurred vision, memory/cognitive impairment, and skin laceration.

*Gabapentin*³⁰⁶² (Neurontin, Rangabax): Although structurally resembling GABA it has no direct effect on GABA. Has its own CNS binding site ($\alpha 2$ - δ subunit of calcium channels) and does not interact with the GABA receptor. It is used as an add-on drug for partial seizures, with/without secondary generalisation. Mood stabilising properties are poor, although a role as an anxiolytic (e.g. in social anxiety disorder) has been suggested. It may relieve some cases of tardive dyskinesia. (Hardoy *et al*, 1999) It was said to have

³⁰⁶¹ CRMP-2 is a phosphoprotein mainly found in neural tissue and has a role in neuronal differentiation and the control of axonal outgrowth.

³⁰⁶² Short half-life of 6 hours.

analgesic effects in people with neuropathic pain, possibly by an action on N-type calcium channels, but marketing forces may have been at play here (see Landefeld & Steinman, 2009). It can cause sedation, fatigue, ataxia, dizziness, nystagmus, headache, tremor, nausea and vomiting, diplopia, amblyopia, rhinitis, pharyngitis, dysarthria, nervousness, dyspepsia, amnesia and myalgia. Rare associations include pancreatitis, increased liver enzymes, erythema multiforme, Stevens Johnson syndrome, and (of unproven association) unexplained death. There are no major interactions. Avoid during pregnancy or lactation. Avoid antacids because they reduce gabapentin absorption.

Tiagibine (Gabitril): A nipecotic acid derivative that specifically inhibits GABA uptake (at GAT1 GABA transporter) into neurones and glia. An add-on therapy for partial seizures, with/without secondary generalisation, it does not interact with oral contraceptive drugs, and predictable effects are due to linear pharmacokinetics. Plasma level monitoring is not required.

*Topiramate*³⁰⁶³ (Topamax): This drug selectively blocks glutamate receptors, is a calcium antagonist, it potentiates GABA, and it inhibits carbonic anhydrase. Topiramate, an add-on therapy for epilepsy, has a spectrum similar to phenytoin or carbamazepine. There is an associated risk of renal calculus³⁰⁶⁴ (espc. if combined with other carbonic anhydrase inhibitors such as acetazolamide³⁰⁶⁵). Dose-related cognitive impairment may occur. *Acute myopia and secondary angle-closure glaucoma* have been reported, typically within first month of therapy (acute onset of decreased visual acuity and/or ocular pain with myopia, redness, shallow anterior chamber, raised intraocular pressure with or without mydriasis: stop the drug quickly and treat any raised intraocular pressure). Weight loss may occur as may metabolic acidosis. It has been used as adjunctive therapy in bipolar disorder, e.g. it may reduce weight gain when combined with olanzapine (Vieta et al, 2004); however, evidence for efficacy of topiramate in mania is lacking. (Grunze, 2009)

Levetiracetam (Keppra): This S-enantiomer pyrrolidine derivative is available for persons over 16. It is employed as adjunctive treatment for partial seizures with or without generalisation. Unknown mode of action, but GABA is involved. Side effects include somnolence, asthenia, dizziness, agitation, hostility³⁰⁶⁶, emotional lability, depression, ataxia, and (rare) psychosis. No drug interactions to date. (Anonymous, 2002b)

Zonisamide (Zonegran): A sulfa drug that blocks sodium channels and T-type calcium channels. Weight loss may occur (due to carbonic anhydrase inhibition). It is used for difficult-to-treat partial epilepsy. Zonisamide causes renal stones in 2-4% and it carries a small risk of Stevens Johnson syndrome.

Pregabalin (Lyrica): Used as adjunctive therapy for partial seizures and for anxiety disorders, fibromyalgia, and neuropathic pain of diverse aetiologies. Pregabalin is related to gabapentin. It is more selective on $\alpha 2\text{-}\delta$ subunit of calcium channels than gabapentin.

Felbamate (Felbatol): This appears to work on NMDA and GABA receptors. It is used in USA and one specialist Irish centre for refractory epilepsy. (Kearney & Delanty, 2009) It can cause stimulation. Aplastic anaemia and severe liver damage have been reported.

Treatment with drugs (see preceding notes)

- (a) Generalised – tonic +/- clonic – carbamazepine, sodium valproate, phenytoin
 - simple absence – sodium valproate, ethosuximide
 - complex absence or atonic – sodium valproate, clonazepam, clobazam (Frisium)
 - infantile spasms – ACTH/steroids, clonazepam
- (b) Partial - simple, complex and secondarily generalised – carbamazepine, sodium valproate, phenytoin
- (c) Second line drugs include phenobarbitone, primidone, clonazepam, clobazam, vigabatrin, and lamotrigine.
- (d) Depression in epilepsy – SSRIs are the drugs of first choice but they may interfere with anticonvulsant levels (sertraline and trazodone may be safer in this regard); start low and go slow; and consider need to increase anticonvulsant drug dosage when adding an antidepressant. Maprotiline and bupropion (especially if dose > 450 mgs/day and in eating disorders) can be particularly epileptogenic.

³⁰⁶³ A carbohydrate derivative of fructose, it was proved to be of limited value in treating diabetes.

³⁰⁶⁴ The risk is about 1.5%. Keep the patient adequately hydrated. The cause is carbonic anhydrase inhibition.

³⁰⁶⁵ Acetazolamide is a sulphonamide.

³⁰⁶⁶ Potentially this may lead to assault.

- (e) Neuroleptics in epilepsy³⁰⁶⁷:
- Avoid clozapine³⁰⁶⁸, chlorpromazine and loxapine (highly epileptogenic)
 - Haloperidol is drug of choice
 - Risperidone or sulpiride suitable for longterm use
 - Trifluoperazine, fluphenazine, zuclopenthixol, molindone, and thioridazine are second choice agents
 - Combinations of neuroleptics increase risk of seizures
 - Start low and titrate slowly
 - Monitoring blood levels of combined neuroleptic-anticonvulsant therapy may help
 - If psychosis is attributable to an anticonvulsant, change the anticonvulsant
Anti-epileptic drugs during pregnancy (Tomson & Hiilesmaa, 2007)
 - Cause slight increase in malformation rate
 - Avoid valproate unless it is the only drug that controls the seizures
 - Use monotherapy and lowest effective dose
 - Compliance is paramount
 - Measure serum level at least during each trimester
 - Use folate prophylaxis (up to 5 mg/day)

Surgery is used for patients not responding to optimal drug therapy and for whom the epilepsy is intolerable. The patient/guardian must understand the issues involved, seizures should be disabling despite appropriate medication trials (at least 2 different drugs) and not be due to idiopathic generalised epilepsy, and tests results must suggest that surgery will be helpful (an epileptogenic zone should be identified so that just the right amount of tissue is resected). Comprehensive presurgical evaluation³⁰⁶⁹ is not always readily available and patients often come to surgery after many years of epilepsy. This delay, added to long waiting lists, does not help to improve seizure and functional outcomes. Procedures include focal resection of epileptic tissue, modified hemispherectomy, corpus callosectomy, stereotactic procedures, and multiple subpial resections. (see Shorvon, 1991) The latter procedure, used when onset of seizure activity arises in areas of exquisite cortex, involves multiple cuts that preserves vertical but reduces lateral neural transmission, i.e. it preserves columnar pathways. Multiple subpial resections are effective for Landau-Kleffner syndrome. The lower the IQ the more likely is pathology to be diffuse and the less likely is there going to be a good outcome from surgery. About 60% of patients are seizure free at 10 years post-surgery compared to 5-14% who are not operated on. (Ryvlin & Rheims, 2008) Experienced centres experience a 1% rate of neurological impairment from infectious or vascular causes.

Complications of temporal lobectomy

Death (< 0.5%)

Visual field defect (usually asymptomatic; symptomatic in 15%)

Transient diplopia (common with en block resection)

Persistent hemiplegia (2%)

Psychiatric disorder (2%)

Persistent dysphasia (1%)

Memory impairment (rarely severe; lesser degrees are common)

Chronic and excessive protectiveness over many years by carers may jeopardise post-operative function despite lack of seizures.

³⁰⁶⁷ Benzodiazepines may suffice for post-ictal psychosis. If antipsychotics are used they should be stopped when symptoms abate.

³⁰⁶⁸ This is not an absolute injunction. (Langosch & Trimble, 2002) If clozapine is used it should be commenced in hospital. Combined with carbamazepine it may cause agranulocytosis, or sedation and weight gain if used with valproate. Lamotrigine and clozapine may be preferable.

³⁰⁶⁹ Detailed personal and collateral history and physical examination, interictal EEG (including videotelemetry), MRI, PET, ictal SPECT, and magnetoencephalography are useful. The intracarotid amygdala (Wada) test can be used to determine language dominance, although fMRI may eventually displace the Wada. Intracranial EEG recordings (subdural grid to locate superficial epileptogenic zone [EZ]; depth electrodes [including stereo EEG] to detect deep EZ) are often necessary. Electrical stimulation of a suspected EZ may reproduce the ictus.

Vagal nerve stimulation, used for intractable epilepsy, involves placing a small computer in the chest wall with electrodes sitting on the vagus nerve. A hand-held magnet can trigger intermittent pulses if an aura is experienced. Efficacy may depend on impulses travelling back to the brain³⁰⁷⁰. It is suggested that it may reduce seizure frequency by about 30%.

Transplantation surgery: Phenytoin and phenobarbital may reduce immunosuppressant drug levels with the risk of precipitation of graft rejection. Carbamazepine and gabapentin are the preferred drugs for seizures in such cases. (Surman & Prager, 2004, p. 666)

Interventions during a seizure: Ensure a patent airway. Only move the person if there is danger (e.g. fire) and *do not insert anything in the mouth*³⁰⁷¹ (tongue biting occurs immediately a seizure starts and tongue-swallowing is a myth except with partial seizures arising in the Sylvian region³⁰⁷²). When the fitting stops put the person in the semi-prone position and stay with him/her until all drowsiness and confusion clears. Recurrent or prolonged seizures require medical intervention: airway, O₂, and IV anticonvulsant such as 10 mg diazepam if necessary. Aetiology (including anticonvulsant levels) may need investigation.

Dangerous activities: Anything that poses a danger should be discouraged until over 6 months seizure-free, e.g. cycling.

Notes on driving

*Republic of Ireland*³⁰⁷³

- Pattern of nocturnal seizures only must be established for 12 months before being allowed to drive a car

*UK*³⁰⁷⁴

- Do not drive until no seizure for 12 months after a single seizure
- Epileptics must have no seizure for 12 months or, in the case of exclusive nocturnal attacks, none for 3 years; no driving during withdrawal of anticonvulsants and for 6 months after withdrawal
- Heavy goods/public vehicle drivers not allowed a licence if any seizure after 5 years of age unless off medication for over 10 years with recurrence and must have no epileptogenic cerebral lesion
- It is recommended that one should not drive during withdrawal of medication after seizure remission or for 6 months thereafter
- Any seizure means one can never be an airline pilot

EU

- Permission to drive in one state may not apply in another state

USA

- No consensus on when a patient with *dementia* should stop driving, some experts saying immediately, and others suggesting that the mildly demented are safe driving slowly in familiar, well-lit environments (APA, 2002)

Tumours affecting the CNS

The commonest cerebral tumours in adults are metastatic and are often multiple and widespread. Since the annual incidence of primary tumours of the CNS in the UK is 6.6/100,000 of the population, they are bound to overlap with psychiatric disorders. One French study in the 1960s found that 1/200 admissions to a psychiatric unit had a brain tumour. In childhood primary CNS tumours are the second commonest malignancy after the leukaemias. Interestingly, a low grade tumour is more likely to present with a seizure than is a rapidly infiltrating neoplasm. Ross *et al* (2003) found that of survivors of cancer in childhood and

³⁰⁷⁰ Nucleus solitarius in the brainstem, hippocampus and cortex.

³⁰⁷¹ A tooth may be broken by people putting a spoon or depressor into the mouth with the danger of aspiration.

³⁰⁷² Here, tongue involvement carries a risk of aspiration. The usual victim is a sleeping adolescent.

³⁰⁷³ Psychiatrists are poor at documenting advice given to patients re the effects of treatment and symptoms on driving. (Langan, 2009)

³⁰⁷⁴ See Shorvon (1995) and Beghi and Sander (2005) for Britain and Europe.

adolescence only survivors of brain tumour had an increased risk of hospitalisation for a psychiatric disorder.

Brain tumours can lead to compression symptoms, meningitis, dementia, cerebellar degeneration, degeneration of posterior root ganglia, peripheral neuropathy, and myopathy. The tumour may be wholly outside the CNS in many instances. Depression³⁰⁷⁵, delirium and dysmnnesia are also found in association with malignant disease. Tumours causing abulia are most often found to affect the frontal lobes. Abulia may respond to methylphenidate or dexamphetamine.

Panic attacks are not uncommon presenting features of brain tumours, including tumours of the pituitary gland. Limbic system involvement may be associated with a clinical diagnosis of 'schizophrenia'. A detailed clinical history and a careful physical examination are still the best predictors of brain pathology. CT is the usual first neuroimaging technique employed, although MRI allows better visualisation of the posterior fossa, i.e. use CT if tumour resides above the tentorium and MRI if the tumour lies below the tentorium. In practice, the yield of abnormal results is small. Patients who need a thorough investigation include those who have intellectual deterioration, impaired consciousness, unexplained personality changes of 'frontal lobe' type, and suspected increase in intracranial pressure.

Steroid therapy may cause irritability, insomnia, lability of affect, and psychosis. Whilst dexamethasone-induced mania often abates quickly, prolonged attacks may occur and necessitate lithium or anticonvulsant drug therapy. Dexamethasone may cause insomnia, delirium, psychosis, peptic ulceration, myopathy, osteopenia, or increase the risk for *Pneumocystis carinii* pneumonia. Radiotherapy may cause acute cognitive dysfunction or a sub-cortical dementia that may not present for months or even decades.(Armstrong ea, 2002) Radiation is most likely to cause memory dysfunction in the elderly and in those receiving high doses. Chemotherapy rarely causes cognitive dysfunction when employed to treat primary brain neoplasia. Debulking³⁰⁷⁶ can improve psychological function, although oedema may need to resolve before this becomes obvious. However, frontal lobe lesions are a risk attached to such interventions.

Prolactinoma: These are benign neoplasms, accounting for 40% of pituitary tumours. Over 90% are small and intrasellar. Prolactinomas are divided into microadenomas (<10 mm in diameter) and macroadenomas (>10 mm in diameter). Prolactin levels are highest with the larger tumours. Hyperprolactinaemia can cause infertility and gonadal dysfunction.

Normal prolactin levels³⁰⁷⁷ in females and males are <25 and <20 µg/L respectively. Levels rise 10 times in pregnancy. Drugs rarely raise prolactin levels above 100 µg/L.

Idiopathic hyperprolactinaemia should be followed up in case small tumours are missed.(Schlechte, 2003) Premenopausal females may develop amenorrhoea³⁰⁷⁸ and infertility, and 80% have galactorrhoea.

Hyperprolactinaemia may be detected after stopping the anovulant pill, but there is no evidence incriminating the anovulant pill to prolactinoma formation. Headache and neurological signs are rare.

Tumours tend to be larger at time of diagnosis in males. There may be cranial nerve signs, loss of vision and hypopituitarism. Although rarely present at the start, impotence, infertility, and decreased libido can occur, and galactorrhoea and gynaecomastia are uncommon.

Reduced spinal bone density occurs with prolonged hyperprolactinaemia in both sexes, and a return of prolactin levels to normal leads to increased but still reduced bone density.

A single prolactin level documents hyperprolactinaemia but, because of the pulsatility of prolactin production, the test should be repeated if prolactin levels are 25-40 µg/L. Most causes of increased

³⁰⁷⁵ Depression was the most important determinant of quality of life in a group of patients with cerebral tumours.(Pelletier ea, 2002)

³⁰⁷⁶ Surgical removal.

³⁰⁷⁷ **Prolactin levels are raised by** craniopharyngioma, acromegaly, granulomatous infiltration of the hypothalamus, large non-functioning pituitary tumours, primary hypothyroidism (some cases), hepatic cirrhosis, chronic renal failure (reduced clearance), exercise, meals, stimulation of the chest wall or breast examination, chest wall neoplasia, herpes zoster, polycystic ovarian syndrome, physical or psychological stress, amoxapine, metoclopramide, phenothiazines, butyrophenones, risperidone, olanzapine (transiently), SSRIs, verapamil, reserpine, methyl dopa, oestrogen (as in the oral contraceptive pill), cannabis, and cocaine. Aripiprazole may normalise haloperidol-induced hyperprolactinaemia whilst the patient remains on haloperidol.(Shim ea, 2007)

Macroprolactinaemia: prolactin attached to IgA antibody (needs to be distinguished from raised total prolactin by special tests, e.g. gel filtration chromatography) – macroprolactin cannot cross the walls of blood vessels in order to reach tissue receptors – look for this in all cases of hyperprolactinaemia – if not causing a problem (and if monomeric prolactin level is normal) do not investigate.

Disconnection hyperprolactinaemia: pituitary tumour presses on pituitary stalk blocking tonic inhibition of dopamine from hypothalamus on secretion of prolactin.

³⁰⁷⁸ One can have oligomenorrhoea or regular menses in some cases.

prolactin are ruled out with history taking and physical examination, a pregnancy test, and assessment of thyroid and renal function. The ultimate test is MRI.

Microadenomas may not require treatment if menses are regular. Bromocriptine can be used for infertility and a DA agonist or an oestrogen-progesterone combination may be prescribed for amenorrhoea.

For intrasellar macroadenomas one can use bromocriptine for infertility and a DA agonist for amenorrhoea.

For extrasellar macroadenomas bromocriptine and/or surgery is the treatment for infertility, whilst a DA agonist (bromocriptine, cabergolide, quinagolide) and/or surgery can be used for amenorrhoea.

Incidentaloma: This is a non-functioning tumour of an endocrine gland, e.g. pituitary or adrenal.

Pseudotumour cerebri: This condition includes raised intracranial pressure, classically in a young obese woman. Papilloedema, loss of vision, and sixth cranial nerve palsy may be present. Cases are divided into primary (idiopathic intracranial hypertension) and secondary³⁰⁷⁹. Headache, when present, is usually pulsatile. Management of primary cases includes weight loss, repeated lumbar puncture, diuretics, topiramate, emergency steroids to save sight, and surgery³⁰⁸⁰.

Craniopharyngioma: These tumours may affect sight (optic chiasma) and cognition, memory problems not being entirely explicable by raised intracranial pressure. Other reported findings (by some but not all studies) are excessive sleepiness and eating, bouts of aggression, and (often medication-resistant) depression.

Hyperostosis frontalis interna: There are frontal skull hyperostosis³⁰⁸¹, headache, menstrual problems, obesity, and excess body hair (hypertrichosis). Females outnumber males and the disorder may present from adolescence onwards. Some cases have no neuropsychiatric manifestations whereas others may have neurotic or personality problems, or psychosis. Memory problems and dementia have been reported.

Personality change due to a medical disorder

A persistent change in personality may indicate serious pathology. DSM-IV-TR recognises labile, disinhibited, aggressive, apathetic, paranoid, other, combined, and unspecified types. Causes include head trauma, subdural haematoma, tumours or infarction of the brain, disease of the frontal or temporal lobes or the corpus callosum, various dementing disorders, normal pressure hydrocephalus, AIDS, neurosyphilis, CJD, B12 deficiency, manganese or mercury poisoning, limbic encephalitis, metachromatic leucodystrophy, adrenoleucodystrophy³⁰⁸², and granulomatous angiitis. Abulia (mute, lacks motivation and feeling) must be distinguished from depression.

Focal lesions of the hemispheres

Frontal and temporal lesions are more often associated with personality change and psychosis respectively.

Frontal: There may be a grasp reflex (see table), spastic paralysis and ataxia of the contralateral upper limb, anosmia, incontinence and personality change. Damage to the prefrontal area mainly causes mental disturbances ('frontal lobe syndrome'). Damage to the motor/pre-motor area causes limb weakness, incontinence, akinesia, mutism, apraxia, and Broca's aphasia. A variety of factors influence the type of symptoms to be found with frontal lobe lesions, such as localisation, size, type, and course of lesion, as well as premorbid personality and age.

Frontal lobe

³⁰⁷⁹ There are numerous causes, e.g. neoplasm, obstructed ventricles, cerebral vein thrombosis, cardiac failure, COPD, eclampsia (magnesium sulphate reduces fit frequency in eclampsia), sleep apnoea, vitamin A and derivatives, tetracyclines, lithium, withdrawal of corticosteroids, renal disease, hypoparathyroidism, lead toxicity, Lyme disease, SLE, hypertensive encephalopathy, etc.

³⁰⁸⁰ E.g. fenestration of the optic nerve sheath.

³⁰⁸¹ X-rays show thickened inner frontal skull bone table plus exostoses pushing into the cranial cavity.

³⁰⁸² **Adrenoleucodystrophy:** Rare, X-linked recessive (numerous mutations at Xq28 which codes for ALD protein, a peroxisomal membrane component) inherited disorder with adrenal insufficiency and leucoencephalic myeloneuropathy. Defective oxidation of saturated very long chain fatty acids leads to their accumulation. (Moser, 1997) Rarely starts in adults but may present with psychosis, mania, and cognitive dysfunction. Environment (e.g. head trauma) plays a role as identical twins may differ. Controversial proposed treatments include Lorenzo's oil (mixture of glyceryl trioleate and glyceryl trierucate) and dietary fat restriction.

Dorsolateral damage - apathy (right fronto-subcortical in one study of stroke: Brodaty et al, 2005), psychomotor slowing, diminished fluency of speech, perseveration, reduced executive function (organising, sequencing, planning), utilisation behaviour (patients pick up an object and use it continuously until it is removed by another person), and poor abstracting ability

Orbitofrontal damage - labile affect, disinhibition, impulsiveness³⁰⁸³, poor judgement, lack of insight, and poor abstracting ability

Medial lesions - greatly reduced speech output, akinesia, and, sometimes, apathy (Lauterbach, 2000)

Inferior lesions – tumours and other lesions may cause anosmia

With frontal lobe tumours, psychiatric symptoms occur especially with anteriorly placed tumours. Common symptoms are headache, epilepsy, disturbed micturition³⁰⁸⁴ and neurological abnormalities. The symptoms may be paroxysmal. These symptoms are usually present at the time of diagnosis, even in those with early psychiatric problems, and should be looked for. The commonest psychiatric symptoms associated with frontal lobe tumours are impaired consciousness and progressive intellectual deterioration, followed by mood and behavioural disturbances. In some cases, especially with meningiomas³⁰⁸⁵, there may be no neurological symptoms until the tumours are large and causing displacement. These cases may be referred to a psychiatrist because of progressive personality change and intellectual decline. Frontal lobe release reflexes³⁰⁸⁶ are commoner in demented than in non-demented elderly people.

Localised lesions of the hemispheres

Non-dominant

Occipital³⁰⁸⁷ – homonymous hemianopia, hemianopic scotomata, visual agnosia, prosopagnosia³⁰⁸⁸ (poor face recognition), crude visual hallucinations

Frontal – disinhibition, lack of initiative,³⁰⁸⁹ dyssociality, poor memory, incontinence, grasp reflex, anosmia

Parietal - neglect of non-dominant side³⁰⁹⁰, agnosia, homonymous constructional apraxia, spatial disorientation, dressing apraxia, homonymous hemianopia, contralateral tactile/kinaesthetic hallucinations, tactile perseveration³⁰⁹¹

Temporal – poor non-verbal memory, loss of complex hallucinations, musical skills, complex hallucinations,

Dominant

Do.

Do.

Dyscalculia, dysphasia, dyslexia, apraxia,

hemianopia

Dysphasia, dyslexia, poor memory,

homonymous hemianopia³⁰⁹²

³⁰⁸³ This is sometimes demonstrable with a Go-No-Go task, e.g. ‘Tap once when I tap once but don’t tap when I tap twice’.

³⁰⁸⁴ This, contrary to popular belief, does distress the patient.

³⁰⁸⁵ There does not appear to be a specific personality change associated with **tumours of the temporal lobe**. Instead such change may resemble that found with frontal lobe tumours. About one half of patients with tumours of the temporal lobe develop epilepsy. Sudden onset of symptoms such as forced thoughts, dreamy states, terrible fear, depersonalisation, and déjà vu should bring one to consider temporal lobe epileptic aura.

³⁰⁸⁶ Examples are the snout reflex (tap patient's upper lip with a finger so that his lips purse and the mouth pouts forwards), and the grasp reflex (using your own index and middle finger, stroke the patient's palm crosswise or his fingers lengthways: the patient grasps your fingers and cannot let go despite your request that he does so).

³⁰⁸⁷ Other phenomena associated with occipital lesions include palinopsia (images leave persistent after-traces), metamorphopsia (distorted scenes), and polyopia (more than one visual image). If infarction occurs in one occipital lobe (posterior cerebral artery) there will be a homonymous hemianopia with sparing of the macular area (supplied by middle cerebral artery). If the pole of one occipital lobe undergoes infarction there will be a small scotomatous homonymous hemianopia. If both occipital lobes are severely damaged from any cause there will be Anton’s syndrome (QV).

³⁰⁸⁸ This and asimultagnosia (unable to perceive unity of visual scene) tend to occur when there is co-involvement of parietal/temporal lobes.

³⁰⁸⁹ Incontinence is classically associated with bilateral frontal lobe damage.

³⁰⁹⁰ A person with a non-dominant parietal lobe lesion may ignore left turns during a journey.

³⁰⁹¹ The person continues to perceive contact long after contact ceases.

³⁰⁹² Visual hallucinations that occur within a hemianopic field are suggestive of temporal lobe dysfunction.

homonymous hemianopia

Atavistic (primitive) reflexes associated with frontal lobe disease

These are described differently by different authors. They **can** and **often do** occur in normals, but more than one strongly favours abnormality such as AD, multi-infarct dementia, or AIDS involving the CNS.

Glabellar reflex: damage to fontopontine pathways to facial nerve nucleus – Parkinson's disease, Parkinsonism, dementia, cerebral atrophy, frontal lobe tumours – tap glabella from behind head – not common in drug-induced Parkinsonism

Grope reflex: touch hand of patient and latter will reach out for your hand; extreme cases allow the examiner, by successive touching, to guide the patient's hand through space ('magnet reaction') or, indeed, in the absence of touching, there may be automatic groping for objects seen by the patient

Snout reflex: tap nose and look for excess facial grimacing

Sucking reflex: stroke lip and look for pouting/sucking lip movements (normal in babies and gone by 18 months)

Chewing reflex: put tongue depressor in mouth and look for reflex chewing movements

Grasp reflex: stroke palm and patient will grasp your finger (may resist removal of your finger – sometimes, if you stroke the dorsum of his fingers, he will let go)³⁰⁹³

Palmomental (palmar-mental) reflex: scratch palm and watch wrinkling/puckering of chin³⁰⁹⁴ on same side or scratch base of thumb and look for slight downward movement of lower lip and jaw

Common office tests of frontal lobe functioning

- Naming as many animals as possible in 60 seconds (verbal fluency)
- Getting the patient to reproduce various 3 hand positions or sequentially tap with both hands (motor sequencing³⁰⁹⁵)
- Go/no-go tasks ('tap the table once if I tap it once, but do not tap if I tap twice')
- Abstraction (e.g. 'what do a motorcar and a bicycle have in common?')
- Problem solving (e.g. 'there are 12 books on 2 shelves, the top shelf having twice as many books as the bottom shelf. How many books on each shelf?')³⁰⁹⁶

Parietal: spatial disorientation (tendency to get lost), apraxia, aphasia, agnosia, alexia, perceptual rivalry, and contralateral homonymous hemianopia. Non-dominant lesions are likely if there is agnosia or perceptual rivalry. The others are associated with dominant lesions. *Gerstmann's syndrome*³⁰⁹⁷ occurs with dominant lesions: right-left disorientation³⁰⁹⁸, dyscalculia, and finger agnosia with dysgraphia. Gerstmann described a single case in 1924. It has been suggested that all of its components came together by chance. In reality, any combination of the symptoms can be found. The rare post-traumatic (esp. occlusion of posterior cerebral artery³⁰⁹⁹ supply to the dominant hemisphere) *Charcot-Wilbrand syndrome* is sometimes associated with Gerstmann's syndrome: visual agnosia, inability to revisualise images, and partial or complete loss of dreaming.

Astereognosia or tactile agnosia is the inability to identify simple objects placed in the hand with the eyes closed. It usually indicates a contralateral parietal lobe lesion. Autopagnosia, where the patient totally

³⁰⁹³ This must be distinguished from the *magnet reaction* found in catatonic and organic brain disorders: examiner touches patient's palm – as examiner withdraws his fingers the patient's hand follows them.

³⁰⁹⁴ *Mentum* = protruding part of chin.

³⁰⁹⁵ Also called reciprocal co-ordination. Such motor sequencing can be tested by, e.g. the *fist-ring test*: alternatively make a fist and a ring with one hand and then with the other hand.

³⁰⁹⁶ The answer, of course, is 8 and 4.

³⁰⁹⁷ Josef Gerstmann (1887-1969), psychiatrist in Vienna who left for England in 1938 and then USA. Gerstmann described his syndrome in 1924.

³⁰⁹⁸ Test by asking patient to obey commands, e.g. 'touch your right ear with your left forefinger'.

³⁰⁹⁹ The chief manifestations of infarction in the territory of the posterior cerebral artery are contralateral hemianopia +/- visual agnosia, spatial disorientation or visual hallucinations. Depending on the site of damage there may be an amnesic disorder, Anton's syndrome (QV) or alexia without agraphia. The same object may be seen repetitively or a central object may be seen even after it has been removed from view (*visual perseveration*).

ignores or fails to identify a limb or the whole contralateral side of the body, is due to a more extensive lesion.

Temporal: elaborate visual sensations, epilepsy, hallucinations (auditory, gustatory, and olfactory), illusions, receptive aphasia (with dominant lesions), transient amnesias, homonymous upper quadrantanopia, and *déjà vu*.

Occipital: crude visual hallucinations with irritative lesions, contralateral homonymous hemianopia with destructive lesions.

Corpus callosum: apraxia of left hand, anomia for objects held in left hand, and alien hand syndrome. Paranoid thinking and koro have also been reported (Durst & Rosca-Rebaudengo, 1988).

Agenesis of the corpus callosum³¹⁰⁰: This may be complete or partial. There is a genetic cause in a minority of cases and an association with trisomy disorders³¹⁰¹ is well known. Some cases are attributable to intrauterine toxin exposure or infection to metabolic disorders such as excess glycine. Whilst the condition is usually reported in childhood it may be discovered at any stage of life, even at autopsy. Complete absence may be associated with hydrocephalus and a variety of CNS abnormalities³¹⁰². Seizures, spasticity, intellectual disability (only when there are other malformations), and hydrocephalus are reported associations. It seems that the brain is able to compensate for the absence of this structure in many cases, e.g. by increased use of commissures. *Andermann syndrome*, described in 1972, may run in families and consists of intellectual disability, callosal agenesis, facial dysmorphism, peripheral neuropathy, and psychosis; psychosis may relate to cerebellar atrophy. (Hemmings & Bouras, 2007, p. 207) According to Paul et al (2007) developmental defects of the corpus callosum may be associated with a variety of psychiatric disorders, including depression, schizophrenia, and behavioural problems in childhood, including autistic traits.

Tumours of the corpus callosum: In most cases there is a quick development of intellectual decline, with memory affected first. Personality changes reminiscent of frontal lobe damage may be an early feature. Sleepiness, stupor and diminished activity may indicate diencephalic involvement. Florid psychosis is not unknown and a catatonic picture may be observed.

Head injury

Head injuries³¹⁰³ are one of the commonest reasons for attendance at Irish hospitals. Gloag (1991) reckoned that 70,000 people in Britain suffered from the effects of serious head injury, with an additional 2,000 receiving such injuries each year. 2-5 males are affected for each female. The young male is the classic victim, this group being subject to an excess of road accidents and assaults. Neuropsychiatric manifestations are a more important cause of disability following traumatic brain injury than are neurophysical consequences (Fleminger & Ponsford, 2005) and carer stress may be greater in cases of head injured that with paraplegic partners. (Rosenbaum & Najenson, 1976) Emotional and behavioural sequelae of head injury (e.g. low mood, selfish, irritable, angry, and aggressive) and cognitive difficulties (e.g. difficulty remembering and slowed thinking) in the patient, and poor coping powers, lack of a feeling of being cared for, and radical changes in social circumstances in the carer, as well as lack of money or information feed carer distress. Mixed anxiety-depression (cothymia) is the commonest psychiatric consequence of cranial trauma. The patient with traumatic brain injury (TBI) may grieve for lost functional abilities and may suffer from exacerbations of pre-trauma traits and/or personality change.

Pathophysiology of head injury

³¹⁰⁰ 1:4,000 births.

³¹⁰¹ Trisomy of chromosomes 8, 13, and 18.

³¹⁰² Heterotopia, microgyria, arachnoid cysts, spina bifida, and meningomyelocele.

³¹⁰³ Physical examination details are beyond the scope of this text, e.g. Battle's sign (retro-tympanic blood) infraorbital ecchymosis, and abnormal pupils.

(a) Primary - diffuse axonal damage³¹⁰⁴ - shearing and torsion forces tear axons and support fibres, especially in the brainstem but also caudally; and contusion - especially the frontal and temporal lobes because of bony protuberance and the hard dura

(b) Secondary

Intracerebral (haemorrhage, oedema, subarachnoid haemorrhage, hydrocephalus)

Extracerebral (autonomic changes with failure to compensate for changes in blood pressure and oxygen levels leading to ischaemia and anoxia)

Stretching of nerve fibres may unleash a metabolic cascade that disrupts the blood-brain barrier, interferes with auto-regulation of the brain, causes oedema, impairs metabolism, alters perfusion, disrupts the delicate balance across membranes of ions, activates destructive molecules, leads to free radical generation, and initiates changes in gene expression. Membrane defects near the nodes of Ranvier (*mechanoporation*) and opening of ligand-gated channels by glutamate leads to influx of Na⁺, Ca⁺⁺, and Cl⁻, and efflux of K⁺ ions. Very high levels of K⁺ ions outside the cell inhibit action potentials. Consciousness is lost. Ca⁺⁺ influx activates proteases (calpains and caspases).

A prolonged period of post-traumatic amnesia (PTA), measured from the time of the injury to the resumption of normal continuous memory, is associated with neurological complications³¹⁰⁵, psychiatric disorders and generalised intellectual impairment, and personality change. Retrograde amnesia (for events before the injury) is not a good predictor of outcome. (O'Shea & Condren, 1996)

Post-traumatic syndrome (post-concussional syndrome/disorder, PCS) is more likely to follow minor injuries to the cranium than it is to follow major traumata. It is important to distinguish between symptoms and the syndrome, although the specific symptoms of the syndrome are not universally agreed. Importantly, lack of appropriate control groups makes it difficult to state for certain which manifestations stem from the original injury to the brain. Also, mild traumatic brain injury does not predict PCS. (Bryant, 2008) The retrospective assessment of mild traumatic brain injury creates interpretation problems of its own. (Fear ea, 2009) PTSD symptoms often overlap with those of PCS (Bryant & Harvey, 1999) and post-concussional symptoms are more likely in the presence of depression or PTSD. Also, the manifestations of PCS overlap significantly with those of somatoform disorders. In practice, symptoms of PCS vary enormously between patients and the same symptoms are common in people without a history of head injury.

ICD-10 PCS

Head injury + at least 3 of 8 symptoms

DSM-IV PCS

Significant cerebral concussion + duration of symptoms > 3 months + symptoms start/get worse post-injury + some cognitive dysfunction

PCS

Headache

Dizziness³¹⁰⁶

Abnormal fatigability

Insomnia

Sensitivity to light and noise

Irritability, anxiety, depression, poor concentration and memory

Some degree of intellectual impairment

Decreased tolerance for alcohol³¹⁰⁷

³¹⁰⁴ It appears that when the injury occurs the axolemma is stretched and compressed. Calcium enters the axon and activates proteases. Proteases damage microtubules and neurofilaments leading to accumulation of products normally transported by these structures. The result is swelling of the axon, lobule formation, and division of the axon with development of a 'retraction ball'. This process takes 24-48 hours to reach completion. Over the ensuing weeks/months there is sprouting from the proximal segment, an attempt at repair.

³¹⁰⁵ E.g. dysphasia, motor disorder and persistent memory and calculation problems.

³¹⁰⁶ Otological damage predicts later dizziness.

³¹⁰⁷ The person gets drunk easily. Some people will drink more because of disinhibition or stress.

Vasomotor instability
 Impaired sexual interest and performance

Risk factors (Fann ea, 2007, pp. 416-8)

Female
 Older
 Previous traumatic brain injury (TBI)
 Psychological stress
 Lack of social support
 Poverty
 Current litigation (but see below)
 Severe depressive symptoms

PCS has a complex aetiology. Early symptoms may owe more to physical factors whereas prolonged complaints may have a psycho-social colouring. Fenton ea (1993) found that while young men were most at risk for minor head injury that older women were most at risk of chronic sequelae. They also found that the emergence and persistence of the 'post-concussional syndrome' were associated with pre-injury social problems. Anxiety and 'compensation neurosis' may contribute to Miller's 'accident neurosis'. (Miller, 1961). In one 3-month follow-up of 60 randomly selected cases of closed adult civilian injuries, 80% had a neuropsychiatric problem midway in the study, 43% having PCS. Pre-injury intensity of neurosis predicted the level of post-accident complaints. Tarsh and Royston (1985) traced and followed 35 claimants in a domestic setting with accident neurosis from 1 to 7 years after compensation was received. Few had recovered and any recovery that did occur seemed unrelated to the time of compensation.³¹⁰⁸ Over-protection by relatives appeared to prolong symptoms. The authors noted that the legal process and the delays involved caused great distress. (see also Cassidy ea, 2000) Fleminger (2009a, p. 195) points out that impending litigation may intensify and prolong disability but that the mechanism behind this is rarely fully conscious. Also, conflictual advice, capital outlay, and having to repeat complaints to a number of specialists heighten frustration and anxiety. The nature of the legal process (adversarial tort versus no fault) may complicate matters. Also, there may be less motivation to complain of symptoms in countries where there is little possibility of financial compensation. Fleminger (2009a, p. 198) writes that overestimating pre-morbid health is common to all injured patients.

The syndrome of 'post-concussional' or 'post-traumatic' dysfunction is not static. It changes over time. Symptom decline is most dramatic during the first week after injury. Anxiety is most likely to be found in cases lasting longer periods. A complex interaction of factors is at work. Organic factors are more obvious in early complainers, psychological ones in later complainers. However, medicine is a clinical, one-to-one, doctor/patient affair, and, whilst generalisations may be true, the individual should be examined for his own sake.

Watson ea (1995) followed up minor head injury cases. Perceived levels of stress at the time of injury, and afterwards, did not relate to symptom formation. Chronic symptoms were associated with continuing brainstem dysfunction.³¹⁰⁹ The degree of transient cortical dysfunction appeared to relate directly to the intensity of early organic symptoms. Fann ea (2004) found the prevalence of any psychiatric disorder in the first year after moderate to severe traumatic brain injury (TBI) to be 49%, 34% after mild TBI, and 18% in unexposed, matched comparison subjects.

In an Australian study of (any) trauma victims (Bryant ea, 2010) at one year 31% reported a psychiatric disorder and 22% developed a psychiatric disorder that was novel for the sufferer, the commonest new disorders being depression, GAD, PTSD, and agoraphobia; PTSD, panic disorder, social phobia and agoraphobia were more likely with a history of mild TBI; but functional impairment, and not mild TBI, was associated with psychiatric disorder. Interestingly, Yaffe ea (2010) found that PTSD among US veterans attending medical centres were at almost double the risk of developing dementia compared with those without PTSD. Is PTSD a cause of dementia, does it damage the hippocampus, is damage caused by

³¹⁰⁸ Similar findings were reported by Deb ea.(1999)

³¹⁰⁹ Pinkston ea (2000) found that many post-concussive symptoms predicted performance on neuropsychological tests better than did mild TBI, a finding against an organic aetiology.

cytokines or cortisol or homocysteine, does PTSD unmask dementia, is the connection explained by cryptic TBI, or is the finding spurious? Were they drinking excessively?(Thomas ea, 2010)

The classical syndrome is seen less frequently in childhood, although head injury is common in childhood and accounts for 25% of all traumatic deaths in children less than 15 years of age. Severed neurones may heal³¹¹⁰ but develop incorrect connections, which may cause persistent sensory abnormalities and major problems in processing multiple stimuli, e.g. concentrating on a lesson when there is much ambient noise. New learning skills are affected more than memory for already learned facts and skills³¹¹¹. The child may be said to be 'lazy' and have social problems³¹¹² and secondary emotional problems. Skilled and repeated assessment should be supplied for such children.

The most troublesome long term morbidity after head injury is caused by behavioural and emotional consequences, including sexual inhibition, aggression, apathy, anxiety, and lability of mood.

Syndromes that may follow local injury (McClelland, 1988)

Frontal - disinhibition, euphoria, reduced vitality

Temporal – aggressiveness

Basal - reduced spontaneity and vitality

Other psychological changes - anxiety, depression, tension, fatigue, irritability, obsessionality, and hypochondriasis

According to Fleminger (2009a, p. 209) aggression after head trauma is associated with being younger when injured, being depressed, frontal injury, and premorbid antisocial behaviour. Lack of confidence, hopelessness, and self-deprecation may be more reliable symptoms than biological complaints (e.g. disturbed sleep) when diagnosing depression in head injured patients.

Post-traumatic seizures can be divided into immediate (seconds/minutes), early (within 7 days), and late seizures. The earlier the seizure onset the more benign is the prognosis for epileptic progression. The vast majority of seizures will occur during the first week. The frequency of *epilepsy* following head injury varies from 0.75 - 2.5% in peacetime to 45% in wartime³¹¹³. Penetrating injuries and injuries affecting multiple cerebral lobes are more likely to lead to epilepsy than are closed injuries or unilobular injury. A history of alcohol abuse increases the risk for post-traumatic epilepsy. The risk of epilepsy following mild or severe brain injury or skull fracture in children and young adults is increased and lasts for years; a family history of epilepsy increases the risk of epilepsy following mild or severe brain injury.(Christensen ea, 2009) Petit mal is rarely, if ever, due to trauma. Antiepileptic drugs are poor at preventing seizures after head injury and phenytoin may even slow recovery.(Hammeke & Gennarelli, 2003, p. 1161)

Evoked potentials measure conduction velocity in the CNS. Central conduction velocity is extremely sensitive to trauma. Information from evoked potentials provide helpful prognostic indicators: the degree of recovery of these central conduction times correlates with clinical improvement.(McClelland, 1988)

SPECT and other functional imaging procedures may show areas of hypoperfusion in cases of mild TBI when structural imaging is negative.(e.g. Korn ea, 2005) However, other causes of hypoperfusion (e.g. schizophrenia or depression) should be borne in mind.

Increased age is associated with a reduced chance of returning to work, increased memory problems, an increased incidence of anxiety and fears, and an increased mortality rate. Chronic high alcohol intake delays reparative processes within the CNS.

Legal liability should be decided early, or a 'no fault' system of compensation should be introduced.

*Reduplicative paramnesia*³¹¹⁴ is a delusion that one is not where one is but is instead in another place. It is often associated with neurological deficit such as that following CVA or head trauma.

Fleminger (2003) reviewed the management of agitation³¹¹⁵ and aggression³¹¹⁶ following head injury.

Fleminger (2003) warns that haloperidol is overused and can cause akathisia and worsening of confusion.

Attention to differential diagnosis is important, e.g. alcohol withdrawal. Beta-blockers are best for agitation

³¹¹⁰ More so in the younger child.

³¹¹¹ Therefore, the smaller the store, the harder it is to catch up.

³¹¹² E.g. difficulty getting on with others, and disinhibition.

³¹¹³ Fleminger (2009, p. 198) states that post-injury epilepsy affects 2-5% of those with closed injuries (where temporal lobe epilepsy is the commonest form) and 30% when there is dural penetration.

³¹¹⁴ Described by Pick in 1903.

³¹¹⁵ Found in 10% of severe cases as part of delirium and tends to cease spontaneously.

³¹¹⁶ Often impulsive and due to personality change.

and aggression but have troublesome side effects. Olanzapine and quetiapine have useful sedative effects. Carbamazepine or valproate may help in the presence of epilepsy or mood disorder. Depression or anxiety may respond to trazodone. Minimum effective doses should be used and the need for continued prescribing should be reviewed frequently. *Reactive nursing* (nurse only gives attention if patient disturbed) may reinforce the problem. According to Fleminger (2003) early transfer to a specialised rehabilitation unit³¹¹⁷ leads to better outcome than delayed stays on medical or surgical units. The availability of such units, especially ones with a high tolerance for disturbed behaviour, may be less than the ideal.

Boxing and head injury: 361 boxers died in the ring worldwide from 1945-1993. Repeated minor blows to the head may be associated with dysarthria, bradykinesia, ataxia, intellectual impairment, morbid jealousy, cerebral atrophy on CT scanning, loss of cortical neurones and neurofibrillary degeneration (*vide infra*), and signs of cerebellar, pyramidal and extrapyramidal damage. There may be perforation of the septum pellucidum. The boxer can look forward to a worsening of all these until he finally quits the ring. Indeed, 15-20% of boxers will develop dementia after a professional career. Boxing must be included in the differential diagnosis of dementia. Blows damage the cortical (especially frontal and temporal) surface and cause multiple disruptions of neuronal networks (*Strich lesions*). Bleeding may occur, especially in the substantia nigra and deep periventricular tissues. MRI has shown generalised cerebral atrophy and many tiny clefts in the hemispheres. 'Punch drunk syndrome' or *dementia pugilistica* consists of slurring of speech, ataxia, dementia and early demise. Plaques and tangles of similar distribution to those in AD are found, but they fail to take up standard silver stains that are employed for AD (*no beta-amyloid neuritic plaques*). Gliosis and atrophy are concentrated in the medial temporal lobe, i.e. limbic system (memory/behaviour). A swinging blow to the jaw causes the head to rotate in the vertical plane. Head guards do not protect from rotational injuries, only making the head a bigger target. Eye injuries are common – retinal tears and drainage abnormalities. Boxing has been banned in a number of Scandinavian countries.

Loosemore *et al.* (2007) found no evidence for chronic traumatic brain injury in the literature on amateur boxing although the 'quality of evidence was generally poor'.

McCrory (2003) concluded that head to ball contact in soccer is unlikely to cause brain injury but head to head contact, which is difficult to prevent, might do so.

A direct and active therapist stance is necessary. The environment of head-injured patients may need modifying in order to minimise disturbed behaviour. Troubling stressors and excessive demands should be avoided. Routine, structure, task simplification, modification of environmental stimulation, and removal of annoyances may be needed. Realistic hope should be instilled, mourning should be assisted, strengths should be identified, and self-esteem bolstered. Anosognosia should not be confused with denial. Memory aids, use of concrete communications, and short psychotherapeutic sessions may help. CBT might help in reducing psychological distress (Tiersky *et al.*, 2005) but more research is required to confirm this. The patient should be taught skills that assist coping, relaxation, and stress management. Problem-solving skills and breaking down goals into achievable ones will assist progress. Options should be rehearsed. Mittenberg *et al.* (1996) reported that participating in education programs aimed at normalising reactions can improve post-concussional symptoms. People who look after the head-injured also need education. They will need to learn the middle road between excessive protection and risk-taking if the patient is to achieve optimal independence and competence.

Headache³¹¹⁸

Childhood headache, which is associated with psychosocial adversity, may be a risk factor for adult headache and psychiatric symptoms in adulthood.(Fearon & Hotopf, 2001)

³¹¹⁷ A structured, open environment, with normal sleep/wake schedule and relief of boredom.

³¹¹⁸ Headache is also known as cranialgia or cephalalgia. Whereas all pain is felt in the brain, brain parenchyma is pain insensitive. Structures above the tentorium are innervated by the ophthalmic division of the V cranial nerve, whilst structures below the tentorium are innervated by C2 and C3. Cerebellar lesions usually cause pain posteriorly, and pain from occipital lobe lesions is felt anteriorly. A careful history (e.g. past headaches) and a physical examination (e.g. for focal signs) are important. However, because of a contribution from the caudal nucleus of V nerve, pain from upper cervical spine or posterior fossa can also be referred to the front of the head.(Evans & Mathew, 2005, p. 3)

Causes of headache (partial list: see Headache Classification Subcommittee of the International Headache Society, 2004)

Trauma, post-coital, post-tussive, sneezing, sinusitis, cervical spondylosis, carcinomatosis
*Lumbar puncture*³¹¹⁹

Drugs: alcohol, caffeine, nicotine, nifedipine (calcium antagonist), glyceryl trinitrate (GTN)³¹²⁰, hydralazine (vasodilator), indomethacin, dipyridamole, ergotamine, and antidepressants

Dental: impaction, infection, and malocclusion

Ophthalmic: glaucoma, refractive error, and retrobulbar neuritis

Increased intracranial pressure: tumour, abscess, haematoma, benign intracranial hypertension (idiopathic intracranial hypertension, pseudotumour cerebri), infection (e.g. encephalitis), and cerebrovascular accident (10% of cases of polycystic kidney disease have intracranial saccular aneurysm)

Skull: Paget's disease

Haematological: anaemia, hypoxia, and hypercapnia (pulmonary)

Cardiovascular: migraine, hypertension³¹²¹, influenza and other systemic infections

*Psychogenic*³¹²²: tension, depression (Wang et al, 1999)

Endocrine: Hypothyroidism³¹²³, Addison's and Conn's diseases, pheochromocytoma

Inflammation: meningitis³¹²⁴, subarachnoid haemorrhage, systemic infection, and cranial arteritis

Medication-overuse headache

Chronic headache due to frequent intake of analgesics or triptans (5-HT₁ agonists)

May affect 1% of population

Treatment involves withdrawal of offending drugs and clear restrictions on further use of painkillers

Haemodialysis³¹²⁵

Mild/moderate severity, bilateral, tight/pressure, starts during the procedure

Lasts a few hours

Sometimes severe/throbbing with features of migraine or tension headache

ACE inhibitors may help

Posterior reversible encephalopathy syndrome

Rare MRI finding

Bilateral posterior cerebral oedema

Associated with various illnesses (eclampsia, SLE, hypertensive encephalopathy) and immunosuppressant drugs

Cervical spondylosis

Classically affects older people

Usually early morning headache, because neck is stiff from lying in bed

³¹¹⁹ Post-LP headache is exacerbated by the erect posture so the recumbent position is prescribed for some hours after the procedure +/- analgesics. Headache may persist for many days in some cases. It can be treated if necessary by injecting 20 ml of the patient's venous blood into the CSF, a so-called autologous intrathecal blood patch.

³¹²⁰ GTN may cause headache (can be worse than anginal pain), hypotension, or syncope.

³¹²¹ Most cases of hypertension do not suffer from headache. Headache is more likely with cerebral bleed or encephalopathy. Chronic renal failure may be associated with headache, emesis, and left ventricular failure. Mediastinal obstruction is associated with bursting headache on lying/bending. A collapsing pulse may cause throbbing headache and fingertip pulsation.

³¹²² An old name for severe, blinding headache of supposed hysterical origin was *clavus hystericus*.

³¹²³ The mechanism is unknown and treatment involves giving T4.

³¹²⁴ **Kernig's sign:** flex hip to 90° and then try to straighten knee (positive: pain and hamstring spasm). Brudzinski's sign: flexion of head on chest causes drawing up of lower limbs. Many cases of bacterial meningitis suffer **headache** for months after the initial illness.

³¹²⁵ A few such headaches are due to removal of caffeine by the dialysis, i.e. a withdrawal syndrome.

Tension headache is caused by stress. It is constant and of long duration. It may be absent for long periods. There is usually no response to painkillers. It feels like a tight band around the head or like a weight on the head. It tends to be symmetrical, have a particular distribution (bifrontal, bioccipital, and nuchal), be of mild to moderate intensity, to have a stable intensity, to get worse as the day progresses, to lack features of migraine, and is often of high frequency (sometimes daily). It responds to reduction in stress, psychotherapy, environmental manipulation, alcohol, tranquilisers, etc. NSAIDs, especially aspirin, may be more effective than paracetamol, and amitriptyline and biofeedback-assisted relaxation training may assist in prevention. (Loder & Rizzoli, 2008)

Migraine³¹²⁶ pathophysiology is probably more complicated than simple ischaemia. Evidence implicates oestrogens, 5-HT, neuropeptides (e.g. calcitonin gene-related peptide), brainstem nuclei, periaqueductal grey matter, cortical spreading depression³¹²⁷ of Leao (Leao, 1944), and activation of vasculature supplied by the trigeminal nerve. Nocturnal migraine occurs during REM sleep. Sufferers (migraineurs) have been characterised as 'anxious and neurotic', but, whilst they do suffer an excess of anxiety and depression (probably more than other headache sufferers: Fleminger, 2009b, p. 504), their disorder has profound effects on their lives. Rasmussen (1992) found that people with tension headache rather than migraine had high neuroticism scores on the Eysenck Personality Inventory. Indeed, previous descriptions of migraineurs as being particularly 'neurotic' may have been due to confinement of studies to clinic samples. (Ziegler & Paolo, 1995) The lifetime prevalence is 16% (18% for women, 6% for men). Migraine with aura is more likely to be familial than is migraine without aura, but the likelihood of a latter case having a similarly affected close relative is increased nonetheless. The risk of a child developing migraine is, respectively, 45% and 70% if one or both parents have the disorder. Being pregnant may relieve migraine and two-thirds of cases improve with physiological menopause, the opposite number worsening with surgical menopause. (Evans & Mathew, 2005, p. 231)

Some migraine triggers

High-oestrogen contraceptive pill, menses, ovulation, HRT
Aged cheese, chocolate, monosodium glutamate, aspartame
Reserpine, alcohol, nitrites, nitroglycerin, ranitidine, hydralazine
Stress and removal of stress
Lights, smells, high altitude
Tiredness, sleeping for too long
Hunger
Head injury
Strong physical activity
Changes in weather

60% of cases experience a prodrome lasting hours to days independent of the experience of an aura.

Migraine prodromes

Depression³¹²⁸
Overactivity, irritability, euphoria, restlessness
Photophobia, phonophobia
Hypersomnia
Hyperosmia
Yawning
Food cravings, loss of appetite

³¹²⁶ Migraine affects 15% of UK adults. (Fuller & Kaye, 2007)

³¹²⁷ **Cortical spreading depression** = neuronal and glial depolarisation wave accompanied by decreased nerve cell activity and hypoperfusion spreading across cortex at a rate of a couple of millimetres every second. The same phenomenon can be induced in animal studies by applying a strong solution of potassium. The wave may be preceded by a brief hyperaemic phase, possibly the cause of the lights that occur during an aura. The headache may be caused by meningeal irritation by cytokines and NO released by the wave.

³¹²⁸ According to Samaan ea (2009) found that not only is there a general relationship between headache and depression but also that among patients suffering recurrent headache there is a specific relationship between depression and migraine with aura.

Constipation or loose stools
Neck stiffness

There may be an aura, visual or paraesthetic. Aphasia may occur as part of the aura. Digitolingual paraesthesias (*cheiro-oral syndrome*) are a common part of the aura – numbness and pins and needles start in the fingers of one hand and extend into the arm and face, especially the nose and mouth area ipsilaterally; this usually follows the visual disturbance but uncommonly occurs without it. *Teichopsia* consists of visual hallucinations, especially of battlements, and is characteristic of migraine. (St Hildegard of Bingen, 1098-1179, may have had migraine-induced visions.)

'*Migrainous syncope*' (loss of consciousness) may occur early or late in an episode but tends to come on slowly with a gradual recovery thereafter; much more uncommon is coma, incontinence and seizure. *Delirium* may complicate an attack: there may be different combinations of dysphasia, agnosia, apraxia, amnesia, temporal lobe phenomena (e.g. déjà vu), disorientation, reduced arousal, complex visual and auditory hallucinations, paranoid thinking, and various levels of upset. Should no headache follow, diagnostic confusion is likely!
Disturbed body image may occur at any stage of an attack – bodily components seem bigger (e.g. taller), smaller, twisted, increased in number (including having more than one body), or removed.

Pain is severe and throbbing or non-throbbing, and often arises early in the morning. It can affect one (hemicrania) or both sides of the head. It may be unilateral and then generalise. Headache lasts 4 to 72 hours. Most attacks last less than a day and those lasting more than 72 hours are referred to as *migraine status*. The patient tends to lie down in a dark room (photophobia), may vomit, or faint if standing. The resolution phase is associated with fatigue, irritability, scalp tenderness, depression or euphoria. Pain may be felt in the face and is then often misdiagnosed as being due to sinus problems. In fact most migraineurs may hold this belief. Migraine attacks may be accompanied by psychiatric symptoms and sufferers may have increased rates of affective and anxiety disorders, nicotine dependence, and alcohol or illicit drug abuse or dependence. The lifetime prevalence of anxiety disorder and major depression has been estimated at 54% and 34% respectively in migraine patients (27% and 10% in controls respectively). Having an aura may increase psychiatric comorbidity. Dilsaver ea (2009) found that in patients who were suffering from a major depressive episode, and regardless of patients' polarity, having a family history of bipolar disorder (BP) increased the risk for having migraine headaches. Ortiz ea (2010) found that migraine occurred in 24.6% of BP patients (34.8% BP II v 19.1% B I) and the combination of migraine and BP was associated with an excess of suicidal behaviour, social phobia, panic disorder, GAD, and OCD. Migraine with aura is associated with an increased risk of ischaemic stroke, migraine angina, as well as other ischaemic vascular events such as myocardial infarction, the risk varying by vascular risk factors. (Kurth ea, 2008)

The International Headache Society recognises migraine with (classic migraine – up to 30% of cases) and without (common migraine or *hemicrania simplex*, the most frequent type) aura. However, the same individual may experience attacks of either of these types and even an aura without headache (*migraine equivalent* or *acephalgic migraine*). Seventy percent of people with migraine with aura also get attacks without aura. In older cases without headache the term *late-life migraine accompaniment* may be used. If headaches occur less than twice monthly analgesics may be tried. Acute (abortive) treatments include paracetamol (acetaminophen), aspirin (often with metoclopramide), caffeine, NSAIDs, ergotamine (by nasal spray or *per rectum*), triptans (sumatriptan³¹²⁹, zolmitriptan, etc), parenteral metoclopramide, (Colman ea, 2004) and opiates (very severe cases only). Lane and Baldwin (1997) have raised concerns that triptans (5-HT_{1B/1D} agonism) may cause a central serotonergic syndrome if combined with other serotonergic drugs (MAOIs, SSRIs, TCAs, lithium). In 2006 the FDA warned that there is a risk of serotonin syndrome when triptans are combined with SSRIs or SNRIs but the American Headache Society (Evans ea, 2010), although advising vigilance, states that the evidence does not support these concerns.

³¹²⁹ Combined sumatriptan and naproxen for acute treatment of migraine may be more effective than either drug taken alone. (Brandes ea, 2007)

If headaches occur more often, use preventive treatment. Seizure activity may be precipitated by the aura of migraine, in which case valproate may be useful as an anticonvulsant and migraine prophylaxis. There may be an increased risk for suicide attempts in migraine sufferers. 5-HT receptor antagonists relieve migraine, especially sumatriptan (Imigran) that blocks 5-HT_{1D} receptors and frovatriptan (Frovex) that has affinity for 5-HT_{1D} and 5-HT_{1B} receptors. If the migraine sufferer is depressed, amoxapine or trazodone may be useful because of their high affinity for serotonin receptors. MAOIs (espc. phenelzine) were found to be useful in migraine in the past. Beta-blocking drugs, SSRIs, TCAs, divalproex, gabapentin (but see Landefeld & Steinman, 2009), topiramate (may reduce chronic migraine to episodic migraine: Edvinsson & Linde, 2010), flunarizine, and naproxen are used as prophylactic agents. Botulinum toxin has also been used for this purpose (when attacks last for at least 15 days in every month): injections are given in forehead, sides of neck, and back of neck. Telcagepant, a new calcitonin gene-related peptide receptor blocking drug, does not (unlike triptans) cause vasoconstriction, is probably as effective as the triptans for migraine prophylaxis.(Edvinsson & Linde, 2010)

Suggested approaches to managing migraine (after Goadsby, 2006)

- With failure of analgesics/NSAIDs in acute migraine try oral sumatriptan, rizatriptan, almotriptan, eletriptan or zolmitriptan (naratriptan or frovatriptan for slower effect/better tolerability; ergotamine orally or dihydroergotamine nasal spray for infrequent headache)
- For nausea or problems with taking tablets try sumatriptan or rizatriptan nasal sprays or rizatriptan (dissolvable wafer) or zolmitriptan (dispersible)
- For headache recurrence use ergotamine (rectally), naratriptan or eletriptan; when acute treatments are poorly tolerated try naratriptan or frovatriptan
- For early emesis use sumatriptan suppository or s.c. injection
- For headache related to menses use nocturnal ergotamine orally or oestrogen patches for prophylaxis and triptans or dihydroergotamine nasal spray for treatment
- For rapid escalation of symptoms s.c. sumatriptan or I.M. dihydroergotamine

Complicated migraine means that focal signs and symptoms of the aura persist beyond the headache phase. An aura lasting between 1 hour and 1 week is called *migraine with prolonged aura*. Persistence of signs lasting over 1 week or evidence on a scan of cerebrovascular accident is termed *migrainous infarction*: to make the diagnosis, the infarction must occur during a typical attack of migraine with aura; the usual infarct involves a wedge of posterior occipital lobe; and risk factors include young, female, smoking, and anovulant use.

Chronic migraine (transformed migraine) is the term used for attacks that increase quickly in frequency over at least a three-month period. Depression is common and often severe. Some, but not all, may be due to over-treatment (rebound headache) and such cases need to be detoxified very slowly. Stress may be important in other cases.

Familial hemiplegic migraine (rare, heterogeneous, autosomal dominant, chromosomes 19p13, 2q24) is associated with transient hemiparesis (with sensory, visual, or language dysfunction) preceding headache. A minority are confused during attacks. Most cases have symptoms of basilar migraine. A few cases develop permanent cerebellar signs. Affected genes code for various products, e.g. calcium (P/Q-type) and Na⁺/K⁺ pump.(Dichgans ea, 2005)

Basilar migraine (Bickerstaff migraine), which is more common in youth, is associated with double vision, tinnitus, dysarthria, bilateral paraesthesiae/paresis, impaired hearing, vertigo, and diminished consciousness. There is evidence of brainstem and occipital lobe dysfunction.

Childhood periodic syndromes (e.g. episodic midline abdominal pain) may be due to migraine. Other types of 'migraine' are *ophthalmoplegic* (headache plus diplopia) and *retinal* (attacks of monocular scintillations, scotomata, blindness, and headaches) migraine.³¹³⁰

HaNDL (headache, neurological deficits, and CSF lymphocytosis) occurs in people aged 15-40 years. There is often a migraine history and one-quarter experience a virus-like illness in the weeks before onset. There are a variable number of episodes of varying fleeting neurological deficits (incl. sensory, motor,

³¹³⁰ **Retinal migraine** is either extremely rare or of questionable validity and **ophthalmoplegic migraine** is now seen as a form of cranial neuralgia rather than a form of migraine.(Fleminger, 2009b, p. 501)

dysphasic), headache (moderate/severe bilateral throbbing), and occasional pyrexia. A minority experience migraine-like visual symptoms. The patient eventually recovers completely. CT and MRI are normal. CSF shows lymphocytic pleocytosis and increased protein level, but no oligoclonal bands. Viral studies are negative.

Cluster headache (migrainous neuralgia): This may be due to a disorder of the hypothalamus. Most cases are male, often heavy smokers and drinkers³¹³¹. Affected women often have atypical attacks. It is always strictly unilateral. It usually affects above one eye³¹³², though sometimes it may affect a cheek or even occur close to an ear. It often strikes at the same time each day. It may occur 1-3 times a day. It lasts a few hours (20 mins – 3 hrs, average 45 mins.). It usually occurs daily for 1-4 months and then remits for 6 months - 5 years. The eye often waters and becomes bloodshot. The ipsilateral nostril becomes blocked and may run. Sometimes the patient develops ptosis or even transient ipsilateral Horner's syndrome. A partial Horner's syndrome (minor degree of ptosis and meiosis), transient or permanent, may persist between attacks. Alcohol or aromatics often precipitate cluster headache. Cluster headache, like nightmares, may rouse the patient from REM sleep.

Analgesics have no useful effect. Cluster headache can be relieved by ergotamine given before an attack. If the condition is expected to last for a few weeks, corticosteroids can be used. If it lasts for much longer, use lithium. Treatment of an attack may involve oxygen (100%, 7-12 litres/minute: vasoconstrictive effect and reduces release of calcitonin gene-related peptide), sumatriptan (subcutaneous [6 mg] or nasal), zolmitriptan (nasal or oral), dihydroergotamine, nasal lidocaine, corticosteroids, and various other procedures, e.g. steroid occipital nerve injection. Various compounds have been advocated as prophylactics, e.g. steroids (prednisolone 60 mgs for 5 days; then reduce by 10 mgs every 2 days), lithium (Bussone ea, 1990), pizotifen, methysergide, topiramate, and verapamil (240-960 mg). Percutaneous radiofrequency trigeminal rhizotomy may be useful for chronic intractable cluster headache. Also, stimulation of the occipital nerves with electrodes implanted in the suboccipital region may be useful for chronic intractable cases. (Burns ea, 2007) The latter procedure may be slightly less effective but safer than hypothalamic deep-brain stimulation. (Leone ea, 2006)

The *differential diagnosis of tension, migraine and cluster headaches* is helped by the following facts. Males constitute 9 out of 10 cases of cluster headache (CH – sharp, boring) and 4 out of 10 cases of tension headache (TH - dull), whereas 3 times as many women as men suffer from migraine (MH – throbs, pulsates). CH is felt around the eye, TH is diffuse, and MH can occur on one side of the head, in the temple, the front of the head, or around an eye. The greatest periodicity is shown by CH. CH occurs at least daily for months, MH happens a number a times per month, and TH varies from one attack to a few dozen attacks over a month. CH, the most severe type of the three, is relatively brief. The CH patient moves about whilst MH sufferers lie still, often in a darkened room. A family history, aura, photophobia or phonophobia, nausea or vomiting will favour migraine. Of course there is nothing to stop someone with one of these headache types having, say, a tumour. Also, MH sufferers are more prone to TH. *Secondary (symptomatic) cluster headache* can be due to many intracranial disorders, e.g. parasellar meningioma. The diagnosis should be considered if there is no periodicity to the attacks, if there is some headache between attacks, if response to treatment is unsatisfactory, and if there are neurological signs (apart from miosis and ptosis).

Giant cell arteritis

Disorder of aorta plus its main tributaries

Largest arteries may dilate, dissect, or rupture

Late middle age onwards (most commonly 75-85 years of age)

Skin may be tender over inflamed superficial artery (pain when combing hair)

Thick, non-pulsatile **temporal** (and/or occipital) **artery** may be seen and felt

May be loss of weight, general lassitude, and depression

Delirium, coma, memory problems

ESR is usually raised (raised ESR and C-reactive protein has a 97% specificity)

Biopsy of the temporal artery is indicated in individual cases

³¹³¹ Both alcohol and glyceryl trinitrate can precipitate attacks.

³¹³² The Tolosa-Hunt syndrome, which responds to steroids, consists of pain in the eye area with oculomotor paresis on the same side.

Monocular or binocular visual loss due to ciliary artery involvement
 Patients whose vision is being destroyed often experience visual hallucinations (Nesher ea, 2001)
 Sometimes have ophthalmoplegia, peripheral neuropathy, myalgia and muscle wasting
 May have facial or oral pain with jaw claudication³¹³³ and difficulty opening mouth/protruding tongue
 Arteries elsewhere, e.g. heart and vertebral, may be occluded – infarction (carotid/vertebral)
 Advanced cases may develop scalp necrosis
 Manage with steroids, e.g. prednisolone +/- anticoagulants
 If treated properly, disease tends to remit in months/years

Susac's syndrome (retinocochleocerebral vasculopathy)

Possible autoimmune infarcting disorder described by John Susac during the 1970s
 Classical case is a young woman
 Deafness plus cerebral and retinal microangiopathy, mainly in young women
 Headache, encephalopathy, personality change, dementia
 After a few years there is variable remission +/- recurrences

Sinusitis

Knowledge of anatomy and a search for local signs (e.g. tenderness or non-illumination) should help in diagnosis
 X-rays may be required
 Visualisation of ethmoid and sphenoid sinuses may require CT or MRI

Trigeminal neuralgia

Diagnosed by UK GPs in 27/100,000 people/year (Bennetto ea, 2007)
 Usually occurs in middle to late age
 Considered in most cases to arise from an ectatic blood vessel (usually a branch of superior cerebellar artery) pressing on trigeminal ganglion
 Can herald multiple sclerosis in younger patients
 Occasionally due to tumour of cerebellopontine angle
 Repeated stabs of lancinating pain in one or more branches of trigeminal nerve
Tic douloureux refers to grimacing or facial spasm during attack
 Attacks may be precipitated by stimulation of specific spots (*trigger zones of Patrick*)
 Precipitants include opening the mouth, eating, swallowing, and hot or cold drinks
 Treatment often involves using carbamazepine (give to level of tolerance)
 Ablation has been used employing radiofrequency lesion or cryoprobe
 Rarely, surgery performed in posterior fossa
 If ganglion is destroyed on one side the pain may recur contralaterally
 Can place piece of material between ectatic blood vessel and ganglion
Anaesthesia dolorosa: severe neurogenic pain due to excess damage to facial sensation when treating trigeminal neuralgia

Glossopharyngeal neuralgia

Triggers include swallowing, chewing, coughing, yawning, or talking

Greater occipital neuralgia

Common
 Presents as pain (ache, pressure, throb, or even shooting) lasting minutes to days in various parts of the head, including retro-orbital
 May (or may not) follow trauma to head or neck
 Aetiology varies - nerve entrapment, myofascial, upper cervical facet joints, or posterior fossa lesion

³¹³³ Jaw claudication characteristically occurs whilst eating.

Raised intracranial pressure

Often presents in the early morning
Fades as the day goes on

Meningitis

Onset usually more gradual than for subarachnoid haemorrhage
Fever is common

Subarachnoid haemorrhage (SH)

Risk factors: tobacco, excess alcohol, hypertension, exertion, large/multiple aneurysms, autosomal dominant polycystic kidney disease

10% are familial

May have been a history of 'warning leaks' (headaches)

May be initial transient unconsciousness

Usually conscious when seen

Severe headache of sudden onset (*thunderclap headache*³¹³⁴), as if struck from behind

Meningism may take some hours to develop

May be mistaken for intoxication or 'psychogenic'

CT positive in 86% of cases (free blood in the subarachnoid space shows as hyperdense area)

MRI using fluid-attenuated inversion recovery (FLAIR) pulse sequences gives better pictures than CT (Noguchi et al, 1995)

CT angiography almost as good as conventional angiography

Clear CSF taken < 3 hours post onset of headache does not rule out SH (takes a long time for blood to diffuse throughout CSF) – only do lumbar puncture where CT scan is negative and if the clinical picture is highly suggestive and there are no focal signs, the patient is alert, and platelet count is adequate

High morbidity and mortality – today, 2/3 survive bleed and 1/3 have significant neurological dysfunction

Further bleeding – 2-3% over 10 years following clipping/coiling

There may be evidence of hypopituitarism

Common: anxiety (incl. worrying about recurrences), organic brain syndromes³¹³⁵, major affective disorder

Early complications – delirium, akinetic mutism

Longer term – chronic headache, various degrees of organic impairment (may or may not improve; may be subjective and/or objective – dementia can be severe), dysphasia

Suicide - 10% in one series

Epilepsy – 5% in first year

Coma > 24 hours or heavy alcohol intake are associated with poor outcome

Cerebral ischaemia (due to vasospasm, hypotension, etc) is a common sequel – nimodipine (calcium antagonist) is given for 3 weeks to reduce risk of ischaemia

Hydrocephalus can cause mental deterioration any time after subarachnoid bleed – short-term shunting may be required

Refer to neurosurgeon for angiography and surgery – coiling³¹³⁶ of aneurysms via intra-arterial catheter has largely taken over from clipping

Benign sex headache (BSH) can occur during sexual intercourse or masturbation (or unaccustomed vigorous exercise in unfit persons). Kritz first described *post-coital headache* in a formal way in 1970. There may be a dull, tight or cramping sensation in the occiput or generally, building in severity until orgasm or abruptly starting with orgasm. Headache may occur at other times. BSH is more likely if

³¹³⁴ Also caused by migraine [*crash migraine*], dissection of the carotid artery, and a number of other disorders.

³¹³⁵ Change in personality often includes irritability or emotionality. Cognitive dysfunction and poor psychosocial functioning are common. (van Gijn et al, 2007) Sometimes there is an improvement in personality – one antisocial patient of this author became a warm, affectionate citizen!

³¹³⁶ A coil of platinum is placed within the aneurysm that then evokes reactive thrombosis. Platinum coils are non-magnetic, thus allowing MRI.

attempting intercourse on a number of occasions in close succession, if fatigued, or if stressed. Uncommonly, vascular complications may result from hypertension during intercourse (such as subarachnoid bleeding). However, some post-coital headaches may be due to hypotension. BSH may even affect the passive partner. Frequent headache can often be prevented with propranolol or indomethacin.

Medications and illicit substances associated with sex-related headaches (examples)

Amyl nitrate
Phosphodiesterase-5 inhibitors
Contraceptive pill
Amiodarone
Cannabis
Amphetamines
Cocaine

The *pregnant* headache sufferer with acute migraine may initially try paracetamol followed by ibuprofen if inadequate relief ensues. (Duncan ea, 2008) Combined oral contraceptives should be avoided in women with migraine with aura because of increased risk of ischaemic stroke³¹³⁷. Peri-menstrual exacerbation of migraine may respond to simple painkillers but may require triptans such as sumatriptan. Hormone replacement therapy can potentially exacerbate migraine.

Attention-deficit hyperactivity disorder (ADHD)

ADHD, a heterogeneous disorder, has often excited controversy. (Timimi & Taylor, 2004; Zwi & York, 2004; Anonymous, 2008b) Terminology has changed significantly over time³¹³⁸. (Polanczyk ea, 2007b) ADHD is a DSM-III (and thereafter DSM-IV-TR³¹³⁹) concept whereas hyperkinetic disorder is a (narrower) DSM-II (hyperkinetic reaction of childhood) and ICD concept. (Santosh ea, 2008, p. 782) Many American children who receive this diagnosis might have been designated as conduct disorder in Europe, (Zwi ea, 2000) although Faraone ea, (2003) whilst admitting that DSM-IV produces higher prevalence rates³¹⁴⁰, discovered no significant difference between American and non-American children in terms of prevalence rates for ADHD. Nevertheless, treatment rates for ADHD differ markedly between countries. (Anonymous, 2007a) Goodyer (2008, p. 107) points out that the traits contained in the ADHD concept (inattention, hyperactivity, and impulsivity) could be measured quantitatively (rather than forming a category) since they are not discontinuous with more 'normal' values; however he also admits that the higher values show more heritability and poorer prognosis.

Global use of all medicines for ADHD in children aged 5-19 years rose threefold between 1993 and 2003. (Anonymous, 2007) American outpatient treatment rates for ADHD increased from 0.9 to 3.4 per 100 children from 1987 to 1997. (Olfson ea, 2003) Kessler, (2004) stated that 4.4% of the US population met criteria for ADHD and that patients tended to be in treatment for co-morbid disorders (e.g. depression or alcohol abuse) rather than for the ADHD. According to Popper ea (2003, p. 838) 2-4% of the school population in the US receive psychostimulant medications. The American expansion of treatment was paralleled by an increase in the number of stimulant prescriptions, leading to organised protest meetings³¹⁴¹. A small study from Kentucky found that 5.5% of medical students had received a diagnosis of ADHD, 72% of these receiving the diagnosis while in college. (Tuttle, 2007) Telephone calls to American poison centres concerning misuse of drugs for ADHD increased during the period 1998-2005. This increase paralleled prescription rates for these medications. (Setlik ea, 2009)

³¹³⁷ Relative risk = 8.72. (Duncan ea, 2008)

³¹³⁸ 'Minimal brain dysfunction' was a forerunner of ADHD. (Wender, 1971) ADD refers to 'attention deficit disorder' (i.e. inattention without the overactivity) and may account for a third of ADHD cases.

³¹³⁹ **DSM-IV-TR** states that symptoms must be inconsistent for developmental age and intellectual ability and those symptoms must have lasted for at least 6 months and that some of the impairing symptoms must have been present before age 7 years. Symptoms must impair in at least 2 settings, e.g. school/work and home. Impairment has to be 'clinically significant'. **DSM-IV-TR subtypes of ADHD:** predominantly inattentive (20-30%), predominantly hyperactive-impulsive (<15%), and combined (50-75% of cases).

³¹⁴⁰ However, Simon ea (2009) who found in their meta-analysis that the prevalence of ADHD in adults declined with age suggested that DSM-IV underestimated the prevalence of the condition. They reported a pooled prevalence of adult ADHD of 2.5%.

³¹⁴¹ See <http://www.fightforkids.com>

Polanczyk et al. (2007b) found a worldwide pooled prevalence of 5.29% but Europe and North America differed significantly from Africa and the Middle East in prevalence estimates. However, geography played a limited role in explaining variability, the main contribution coming from methodological factors: diagnostic criteria, information source, and requirement of impairment.

Head injury in early childhood does not appear to cause ADHD. (Keenan et al., 2008) Philipsen et al. (2008) found that ADHD was associated with emotional abuse in childhood and greater severity of adult borderline symptoms. Mcardle et al. (2002) in their study of children in Newcastle upon Tyne, concluded that while conduct disorder occurs against a background of family conflict and poor child-care, hyperactivity, by contributing to a pattern of confrontation-punishment, is sometimes complicated by disturbed social conduct. Early onset of antisocial behaviour may be linked to a variant of the COMT gene, although the effect is interactive with lower birth weight and environment. (Thapar et al., 2005) Low birth weight (LBW) itself may interact with the environment, e.g. Bohnert and Breslau (2008) found attention problems were associated with LBW in urban areas but not in suburban areas. Intrauterine growth retardation (small for gestational age) in very low birth weight subjects confers a risk for behavioural and emotional problems related to ADHD in young adulthood. (Strang-Karlsson et al., 2008) Linnet et al. (2003), in their review of the literature, looked at maternal lifestyle practices during pregnancy and the risk for ADHD in offspring and found a suspicion that maternal smoking may be associated with ADHD and similar symptoms, a conclusion supported by others (Thapar et al., 2003; Fowler et al., 2009; Pringsheim et al., 2009). Researchers (Mick et al., 2002; Burt and Hendrick, 2003, p. 1519) have raised similar concerns about alcohol use by the pregnant mother. Button et al. (2005) suggest that maternal smoking during pregnancy may contribute in independent ways to both to ADHD and antisocial behaviour in offspring. Not all studies agree with the role of maternal smoking or alcohol use in the pathogenesis of ADHD, (Knopik et al., 2005) and gene-environment interaction is known to be complex. (Knopik et al., 2006; Thapar & Rutter, 2009)

Candidate genes that may be associated with ADHD include DRD-4 and -5, DAT-1, DBH, 5-HTT, HTR-1B, and SNAP-25. It is suggested that ADHD may be associated with DNA variation at the dopamine (DA) transporter gene (DAT-1) (Brookes et al., 2006) and DA DRD-4 or -5 gene and this may explain a small part of the known tendency to run in families. (DAT-1 knockout mice show increases in activity levels.) Transmission of different alleles may be stronger in familial v non-familial cases. DAT1 genotype may interact adversely with maternal alcohol use during pregnancy. (Brookes et al., 2006) It may also explain heterogeneity in selective attention in ADHD. (Bellgrove et al., 2009) Drugs like methylphenidate may work by inhibiting the DA transporter (the noradrenergic system may be involved modulating methylphenidate action: Polanczyk et al., 2007a). The DRD-4-7 variant mediates a blunted response to DA and the number of 7-repeat alleles may predict ADHD. This area requires further research and there are some conflicting reports. Van Dyck et al. (2002) found no evidence for altered DA transporter levels in adult ADHD. Thapar et al. (2007) looked at meta-analyses of molecular genetic studies and concluded that the 48-base pair variable number tandem repeat variant in the D4 gene and the CA(n) microsatellite marker in the D5 receptor gene are associated with ADHD whilst results for the 480-bp variable number tandem repeat in the dopamine transporter gene are mixed.

Haberstick et al. (2008) made heritability estimates of 0.3-0.38 for DSM-IV ADHD subtypes in young adults with retrospectively reported childhood ADHD. Knopik et al. (2005), in a study of female twins, found that 86% of residual variance in ADHD risk (after allowing for prenatal and childhood predictors) was due to genetic effects and 14% to non-shared environmental influences. Hudziak et al. (2005) reported that genetic analysis yielded a model that included genetic dominance (48%), additive genetic factors (30%), and unique environmental factors (22%). According to Biederman (2004), who estimates heritability of ADHD at a high 75% (Biederman & Faraone, 2005), the most important risk factor for ADHD is parental ADHD. He lists other factors as cigarette or alcohol exposure, low birth weight, and psychosocial adversity. Children with ADHD have been shown to have higher mean blood lead levels than do their siblings. (Popper et al., 2003, p. 840)³¹⁴²

Goos et al. (2009) found an inhibitory control deficit in children with ADHD and in their parents and suggested that this may represent an endophenotype of the disorder.

³¹⁴² Bouchard et al. (2009) reported that young adults with low lead exposure who had relatively high lead levels were at greater risk for major depression and panic disorder, suggesting that even traditionally 'safe' levels may do damage. One wonders what would be found if other substances were measured, i.e. do you find what you seek with statistics.

Although still subject to debate, there is some evidence that artificial additives, including colourings³¹⁴³ and the preservative sodium benzoate may contribute to hyperactivity in young children. (Bateman *et al.*, 2004; Kemp, 2008) Kemp (2008) suggests that an 'appropriately supervised and evaluated trial of eliminating colourings and preservatives' should be part of standard treatment.

Psychostimulants do not appear to slow cortical development. (Shaw *et al.*, 2009a) According to Flory *et al.*, (2007) lower serotonergic responsivity in childhood ADHD predicts later antisocial personality disorder. PET scanning has shown this latter group to have reduced glucose metabolism globally and regionally (especially in premotor cortex and superior prefrontal cortex, areas involved in control of attention and motor activity) and MRI in boys has found significant differences from controls in right prefrontal-striatal-pallidal structures. MRI in girls and boys has demonstrated significantly smaller volumes in the posterior-inferior cerebellar vermis. Other MRI research found right-sided grey matter deficits that might underlie attentional network disruption and left-sided white matter deficits that could possibly be due to demyelination. Sowell *et al.* (2003) performed MRI on children and adolescents with ADHD (and controls matched for age and sex) and found morphological abnormalities of frontal cortices and reduced regional brain size mainly involving bilateral inferior prefrontal cortex; brain size was bilaterally smaller in anterior temporal cortex; and there were prominent bilateral increases in gray matter in large parts of the posterior temporal and inferior parietal cortices. Castellanos *et al.* (2003) performed MRI on nine pairs of monozygotic (MZ) twins discordant for ADHD and found affected twins had smaller caudate volumes than did their unaffected co-twins. Qiu *et al.* (2009) used MRI and found that boys had small basal ganglia volumes and volume compression of bilateral caudate head and body, anterior putamen, left anterior globus pallidus, and right ventral putamen, as well as volume expansion in posterior putamen, whereas girls with ADHD had basal ganglia volumes and shapes similar to normal controls. Shaw *et al.* (2009b) prospectively followed children with and without ADHD with MRI. In normal development increased dimensions of right frontal and left occipital cortex emerge in the adult from the reversed pattern of cortical asymmetries in the child. Loss of the prefrontal part of such changes in ADHD is in keeping with disrupted function in that area. McAlonan *et al.* (2009b) found that an ADHD group had difficulty inhibiting a prepotent response and took longer to shift to a new response and these reaction times correlated with fronto-striatal-temporal volumes; these volumes increased with age on MRI and older children improved in terms of reaction speed; in particular, better inhibitory control was associated with larger regional grey matter volumes in bilateral anterior cingulate, right basal ganglia, and left medial temporal circuitry. Biederman *et al.* (2008c) found that ADHD and bipolar disorder independently contributed to volumetric changes of separate brain structures in adults. The pulvinar may be small bilaterally in ADHD but it seems to enlarge if stimulant medication is taken. (Ivanov *et al.*, 2010) The same authors (Ivanov *et al.*, 2010) used MRI and found that 8-to-18-year-olds with ADHD with severe hyperactivity had reduced sizes in right lateral and left posterior thalamic surfaces whereas those with severe inattention had increased sizes of right medial thalamic surfaces. In one controlled fMRI study, (Schulz *et al.*, 2004) adolescents with childhood-onset ADHD showed enhanced responses during inhibition in ventrolateral prefrontal cortical areas that subserved response inhibition, as well as in anterior cingulate and frontopolar regions involved in other executive functions. In an fMRI study employing a task requiring withholding of a triggered motor response (see also Pliszka *et al.*, 2006) medication-naïve adolescents with ADHD demonstrated reduced activation in the right inferior prefrontal cortex during successful motor response inhibition and in the precuneus and posterior cingulate gyrus during inhibition failure. (Rubia *et al.*, 2005) Children with ADHD failed to activate the caudate nucleus in one fMRI study involving tests of interference suppression and response inhibition. (Vaidya *et al.*, 2005) Stevens *et al.* (2007) conducted fMRI during an auditory oddball task (tests the brain's ability to attend to odd or novel environmental stimuli) on boys with combined type ADHD (hyperactive and impulsive) and found deficits in areas involved in orienting attention and processing working memory. During a task that measures the underlying neural control of inhibition and stopping (compared to normal boys) Rubia *et al.* (2008), using fMRI, found that during successful inhibition boys with pure ADHD have relatively less activation in the left dorsolateral prefrontal cortex and, during inhibition failures compared to go responses, boys with either pure ADHD or pure conduct disorder demonstrated underactivation of the posterior cingulate gyrus, and pure conduct disorder was associated with reduced temporoparietal activation bilaterally. An fMRI study (Rubia *et al.*, 2009) of male (aged 9-16 years) pure ADHD, pure conduct disorder, and healthy subjects found

³¹⁴³ E.g. tartrazine, sunset yellow, and carmoisine.

a process-related prefrontal dysfunction in both disorders: attention-related dysfunction in ventrolateral prefrontal cortex in ADHD and reward-related dysfunction in orbitofrontal cortex in conduct disorder. Brotman *et al.* (2010) used fMRI during exposure to neutral faces in children with ADHD, bipolar disorder, and 'severe mood dysregulation', as well as normal controls and found that ADHD subjects demonstrated overactivity of the left amygdala whilst the mood dysregulated group showed under activity. fMRI findings also suggest that methylphenidate may normalise activity in the left ventral basal ganglia. (Shafritz *et al.*, 2004)

An MRS study (Stanley *et al.*, 2008) comparing 6-10-year-old with and without ADHD found lower bilateral membrane phospholipid precursor³¹⁴⁴ levels in the basal ganglia and higher membrane phospholipid precursor levels in the inferior parietal region, suggesting aberrant brain development.

A PET study of never-treated adult ADHD subjects and a non-ADHD comparison group (Volkow *et al.*, 2009) evaluated the brain reward pathway in ADHD. The authors found lower levels of DA receptors and transporters in the nucleus accumbens and midbrain, with the most pronounced cases of ADHD having the lowest levels of these proteins in these brain areas.

Neonatal ultrasound abnormalities suggestive of white matter injury in low-birth-weight babies are associated with increased risk for some psychiatric disorders, especially ADHD, at age 6 years. (Whitaker *et al.*, 1997)

It has been suggested that about 50% of hyperactive children will become hyperactive adults. (Toone *et al.*, 1999; Kooij *et al.*, 2005) Meta-analysis of follow-up studies (Faraone *et al.*, 2006a) found that rates of persistence to age 25 years depended on breadth of diagnostic criteria: 15% for full criteria and 65% for partially remitted cases. Hyperactivity and impulsivity seem to attenuate faster than inattention over time in children with ADHD. (Biederman *et al.*, 2000)

Adult ADHD is an impairing and costly disorder. (Kessler *et al.*, 2009) ADHD affects 0.4% of adults (Kessler *et al.*, 2006) and 4% of adults. (Spencer, 2004) A study in ten countries (Fayyad *et al.*, 2007) found ADHD in 3.4% (range 1.2-7.3% - higher in richer countries) of adults, co-morbidity and disability were common, and patients were more likely to be treated for their other problems than for ADHD. Services for adult ADHD in Britain are patchy. (Edwin & McDonald, 2007) According to Fitzgerald (1998) the core symptoms of ADHD of inattentiveness, impulsivity and hyperactivity affect 0.5-1% of adults. There seem to be deficits in executive function related to spatial working memory but unrelated to age or symptoms. These are not present in those patients on psychostimulants. (Barnett *et al.*, 2001) Co-morbidity is common (Biederman *et al.*, 2006): anxiety, opposition, conduct disorder, antisocial personality disorder, alcohol and substance misuse, and marital/occupational/educational problems. Although Spencer (2004) found that 40% of adults with ADHD may have no comorbid disorder, McGough *et al.* (2005) reported significant lifetime psychiatric comorbidity in adult ADHD. Dalsgaard *et al.* (2002) found that Danish girls with a diagnosis of ADHD had a higher risk of psychiatric admission in adulthood compared with boys with ADHD. Although such girls may be less likely to have comorbid conduct disorder than such boys, the risk of psychiatric admission in adulthood is greatly increased by its presence. McCann *et al.* (2000) found that half of adults with ADHD had a history of psychoactive substance use disorders. Biederman *et al.* (2010) followed up ADHD girls into young adulthood and found that they were at high risk for antisocial³¹⁴⁵, addictive, affective, anxiety, and eating disorders. Developmental coordination disorder (motor coordination problems impacting on daily activity/learning) occurs in a significant number of ADHD children. (Kirby *et al.*, 2007) Biederman *et al.* (2008a) conducted a familial risk analysis and found evidence to suggest that the association between ADHD and drug dependence is likely due to variable expression of a common risk for both disorders, but that the association between ADHD and alcohol dependence results from independent transmission of the two conditions. Biederman *et al.* (2008b) followed up subjects for 10 years (mean age 10.7 to 21.7 years) and found that oppositional defiant disorder was associated with major depression, and oppositional defiant disorder increased the risk for conduct disorder and antisocial personality disorder, but only conduct disorder significantly increased the risk for substance abuse, smoking, and bipolar disorder. The same group (Wozniak *et al.*, 2010) found similar rates of ADHD in the families of ADHD and bipolar I children. Langley *et al.* (2010) examined 5-year outcome for a UK cohort of children diagnosed with and treated for ADHD and found that about 70% still had full ADHD, were known to specialist services, and exhibited

³¹⁴⁴ Phosphomonoesters that are anabolic metabolites of membrane phospholipids.

³¹⁴⁵ Lifetime hazard ratio = 7.2 (95% CI = 4.0-12.7) in comparison to age-matched females.

high levels of antisocial behaviour, criminality and substance use problems; maternal childhood conduct disorder predicted offspring ADHD continuity, and maternal childhood conduct disorder, lower child IQ, and social class predicted conduct disorder symptoms in the children.

Whilst it is stated that ADHD is commonly associated with BAD and both complicates its course and interferes with social adjustment, Santosh et al (2008, p. 783) point out that consensus has yet to be reached on the 'existence and definition of pre-adolescent mania'. The co-association of ADHD and lifetime bipolar affective disorder (BAD) has been examined in a Turkish study of 159 BAD patients. (Tamam et al, 2008) 16.3% of BAD cases had adult ADHD. A different 10.7% were diagnosed with childhood (but not adulthood) ADHD. The authors used the *Wender Utah Rating Scale* and a *Current Symptoms Scale* for ADHD symptoms. Only BAD cases with adult ADHD had higher lifetime Comorbidity rates for Axis I disorders (panic, alcohol, etc) compared to cases without lifetime ADHD. BAD with comorbid adult ADHD did not differ from BAD patients with comorbid childhood ADHD in terms of demographics or clinical variables except for adult ADHD scale scores.

The *Utah criteria* (Wender, 1995; Ward et al, 1993) include inability to relax, dysphoria when inactive, restlessness, distractibility and non-completion of tasks, labile mood, impulsivity, transient temper outbursts, excessive or inappropriate reactions to mundane events, and problems in any life area. However, it is argued that these do not provide a diagnosis in adulthood. (Kirley & Fitzgerald, 2002; McGough & Barkley, 2004) However, Reimherr (2006) defended the criteria, arguing that they focus on recalling easily remembered childhood problem areas. Also, a number of authors (e.g. Tamam et al, 2008) continue to use them for adults.

Utah Criteria for ADHD (Wender, 1995)

Childhood diagnosis: DSM-IV criteria (from parents/older siblings) or hyperactivity + attention deficits and 1 of school behavioural problems/impulsiveness/over-excitability/temper outbursts/combined with *Wender Utah Rating Scale +/- Parents Rating Scale*

Adult characteristics: Motor hyperactivity + attentional problems and 2 or more of affective lability/disorganisation/temper outbursts/over-reactive emotionally/impulsive/other axis I diagnoses excluded

The *Connors Teacher and Parents Rating Scales – Revised* and the *Child Behaviour Checklist* are commonly used scales used to evaluate ADHD symptoms.

Problem arises when ADHD was not diagnosed in childhood and an adult psychiatrist is presented with prominent antisocial personality traits. DSM-IV-TR demanded a childhood history of ADHD in order to entertain the diagnosis in adulthood, and DSM-IV-TR does not permit a separate diagnosis of ADHD in the presence of a pervasive developmental disorder (although the patient may meet the diagnostic criteria). DSM has been challenged as being excessively stringent since cases with very late onset are encountered clinically. (see Faraone et al, 2006b, 2009) Dispute notwithstanding, late diagnosis requires corroboration from as broad a number of sources as is practicable, including the family, general practitioner, any existing childhood and school assessments. (e.g. Rey et al, 2007, p. 407)

'Undiagnosed' adult cases may have an excess of depression, problem drinking, lower educational attainment, and many emotional and interpersonal problems. (Able et al, 2006)

The differential diagnosis of ADHD, which has been called a 'diagnosis of exclusion' by Popper et al, (2003, p. 848) is a broad one.

Differential diagnosis of ADHD

Normality (including attention-seeking behaviour), boredom,

Excess psychosocial stimulation or deprivation

Cerebral trauma

Many psychiatric disorders - including posttraumatic stress disorder, mood disorders, oppositional defiant disorder, and conduct disorder

Child sexual abuse

Hunger, constipation, pain

Thyroid diseases

Various drugs/toxins e.g. pseudoephedrine, caffeine, lead, and theophylline

Hyperactivity confined to school should prompt a search for specific remediable problems such as specific learning disorders. Hyperactivity confined to the home should lead to an evaluation of parenting. (Santosh ea, 2008, p. 783) In such cases there may be no need for drug treatment.

Despite earlier teachings, psychostimulants **do not** have a 'paradoxical' effect in ADHD cases. Similar doses have similar effects on cognition and behaviour in normal boys, hyperactive boys and healthy adults. (Cozza ea, 2003, p. 1405)

Pemoline, formerly used for ADHD was withdrawn because of concerns over hepatic toxicity. (Toone ea, 1999; Kooij ea, 2004) The FDA decided in 2006 to have *Ritalin* and *Concerta* (methylphenidate HCL) and *Adderall* (amphetamine) carry a black box warning due to their tendency to cause raised blood pressure and cause tachycardia, with a resultant potential to increase risk for heart attack, stroke, and sudden death.

Novartis circulated a warning in the same year to avoid stimulants in the presence of structural heart abnormalities or severe hypertension. Problems with stimulants are summarised in a box.

Stimulants (e.g. Santosh ea, 2008, p. 785)

About one-third of cases fail to respond to or to tolerate stimulants

Avoid in schizophrenia, cardiac arrhythmias/angina pectoris, glaucoma, and hyperthyroidism

Caution advised with young people, depression, high blood pressure, pervasive developmental disorder, severe intellectual disability, tics/Tourette in family, history of drug misuse

Time (weeks) or drop in dose may decrease common side effects such as headache, irritable mood, tummy pain, and anorexia

Mild appetite suppression is usual: take medication after morning and midday meals, use high calorie snacks, and use lower doses at weekends/holidays

Rebound effects (excitable, overactive, irritable, excessively chatty, and poor sleep- the latter may be drug-induced or related to a return/exacerbation of ADHD - adding clonidine before retiring, reducing/bringing forward last stimulant dose, or a change in medication may improve sleep) may occur at day's end or following abrupt cessation of stimulant

Methylphenidate can usually be used in the presence of well controlled epilepsy

Rare stimulant effects include aggressiveness, psychosis, and hypertension

For reasons that are not clear, there may be a tendency to stop prescribing stimulants as patients with ADHD reach late adolescence and early adulthood (McCarthy ea, 2009)

Different authors suggest that stimulants stunt growth or that growth delay is part of ADHD – baseline measurement of height and weight, repeated at intervals, is a wise approach

Concerta XL is prolonged release methylphenidate³¹⁴⁶ taken once daily in the morning whereas *Equasym* is an immediate release form of methylphenidate³¹⁴⁷ that was launched in 2004. Doses of Ritalin over 5 mg daily are given in divided doses. A mixture of amphetamine salts has improved adult ADHD, at least in the short term. Concern has been voiced over a too broad use of stimulants (Rey & Sawyer, 2003) although stimulant treatment for ADHD has been reported to reduce (or not increase or be neutral) the likelihood of substance abuse. (Wilens ea, 2003; Mack ea, 2003, p. 368; Faraone ea, 2007; Biederman ea, 2008a; Mannuzza ea, 2008)

Atomoxetine³¹⁴⁸ (*Strattera* – 10 mg, 18 mg, 25 mg, 40 mg, and 60 mg capsules) is a non-stimulant treatment for ADHD in persons of 6 years of age and older; it may work by selectively inhibiting the presynaptic noradrenaline transporter³¹⁴⁹.

Atomoxetine

³¹⁴⁶ UK guidelines that methylphenidate should be supervised by 'a specialist in childhood or adolescent behavioural disorders' can presumably be translated into 'a specialist in adulthood behavioural disorders' when treating adults!

³¹⁴⁷ 5, 10 and 20 mg tablets.

³¹⁴⁸ Atomoxetine is mainly metabolised by CYP2D6. Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide, mainly in the urine.

³¹⁴⁹ Lack of cerebral cortical DA terminal DA reuptake sites causes DA to be taken up a noradrenaline reuptake sites, and the resultant increase in prefrontal cortical DA may be the main action of atomoxetine in ADHD.

Take in the morning or, if needed twice daily, a second dose is administered in the late afternoon/early evening

Initial doses for children/adolescents depend on body weight: 0.5 mg/Kg for up to 70 Kg and 40 mg/24 hours if over 70 Kg

Doses in moderate and severe liver insufficiency should be 50% and 25% of usual doses

Dose is not reduced with compromised renal function

Contraindicated for use within 2 weeks of MAOI therapy (or *vice versa*) and in those patients with narrow angle glaucoma³¹⁵⁰

Should be stopped if patient is jaundiced or has abnormal liver tests (rare cases of liver damage reported)

Growth should be monitored, although effects on height are minimal (Crawford ea, 2008, p. 1395)

Possible allergic events – rash (potentially severe), angioneurotic oedema, and urticaria

May get postural hypotension, modest tachycardia and increase in blood pressure, abdominal pain, decreased appetite, early weight loss followed by weight gain, nausea and vomiting, constipation, indigestion, flatulence, flu-like symptoms, rigors, sinus headache, disturbed sleep³¹⁵¹, dizziness, irritability, unstable moods, fatigue/lethargy, decreased libido, hot flushes, dysmenorrhoea, ejaculatory/orgasmic/erectile problems, cold peripheries, urinary retention/hesitancy, and prostatitis

FDA statement, September 2005: 0.4% of children and adolescents on atomoxetine v 0% on placebo experienced suicidal thoughts

Irish Medicines Board statement, October 2006: monitor patients for hostility and emotional lability

Anonymous (2007b): long-term safety not clear; reserve for patients who cannot take or cannot tolerate stimulants

Newcorn ea (2008): atomoxetine (45% response) better than placebo (24%) but not as good as methylphenidate (56%) – however, different people respond better to one or other of the active compounds

Rare: *acute hepatitis*

Co-existing tics are not exacerbated

Action of beta-2 agonists (e.g. salbutamol) on the cardiovascular system may be potentiated by atomoxetine

Drugs affecting noradrenaline³¹⁵² may act synergistically with atomoxetine

Overdose: agitation, hyperactivity, bizarre behaviour, GIT symptoms, mydriasis, tachycardia, and dry mouth

Desipramine³¹⁵³ (> venlafaxine, > other antidepressants) may help, although sudden death has been reported in children³¹⁵⁴. Not all experts believe that TCAs are useful here and some relegate TCAs to second- or third-line status.(Cozza ea, 2003, p. 1413) However, Spencer ea,(2002) in a double-blind placebo-controlled trial in children and adolescents with chronic tic disorder comorbid with ADHD, found desipramine to be well tolerated and to ameliorate both disorders. Fluoxetine may help impulsiveness and aggression if the dose is increased very slowly. Lithium may be used for severe emotional lability or in cases with bipolar affective disorder. Bupropion carries a risk of seizures but does not interact with asthma medications.(Connors ea, 1996) Clonidine and guanfacine (Tenex in USA) may be useful if ADHD is accompanied by tics. Clonidine has also been seen as useful for aggressive symptoms. An ECG is suggested by Hoare (2004, p. 595) because of reports of fatal cardiac arrhythmias. Guanfacine is longer lasting and less sedating than clonidine. Carbamazepine can be useful in resistant cases.(Silva ea, 1996) Adding divalproex to optimised stimulant therapy in children with ADHD and refractory aggression may reduce levels of aggression (Blader ea, 2009) but larger trials are required to determine the size of the reduction.

Behaviour therapy employing contingency principles based on learning theory is advocated although effects may not be sustained once therapy ceases and generalization of learning to new setting may not occur. Cognitive psychotherapy is also advocated but results are contradictory.(Santosh ea, 2008, p. 790) Social skills training works best in peer groups. Parental and teacher psychoeducation and training in

³¹⁵⁰ Increased mydriasis.

³¹⁵¹ EMW and middle insomnia.

³¹⁵² E.g. TCAs, venlafaxine, mirtazepine, pseudoephedrine, and phenylephrine.

³¹⁵³ TCAs in children - monitor for cardiac problems: vital signs and ECGs.

³¹⁵⁴ However, Biederman ea (1995) did **not** find a causal relationship between desipramine and risk of sudden death.

learning theory principles (often modelled by the therapist) may be beneficial. The family might require assistance in changing communication patterns and improving functioning (Barkley et al., 1992) although gains are relatively modest.

Guidance issued by the UK National Institute for Clinical Excellence is summarised in the box.

2008 NICE guidance for ADHD (Kendall et al., 2008)³¹⁵⁵

Diagnosis

Must meet ADHD criteria of DSM-IV or hyperkinetic disorder criteria of ICD-10; impairment is at least of moderate clinical and/or psychosocial significance (taking chronological and mental age into account); symptoms are pervasive (occur in at least two settings); thorough assessment of needs

Treatment

Preschool: offer parents/carers referral to parent training/education programme; drug treatment is not recommended

Teachers of school age children: those trained in ADHD and its management should provide behavioural interventions in class (e.g. token system)

School age child/young person with moderate ADHD: offer parents/carers referral to parent training/education programme (+/- informing school of areas of behavioural management addressed in sessions); offer medication to those who refuse non-drug management or who don't respond to parental/carer training/education programme or group therapy; only a healthcare profession who is appropriately qualified and who is expert in ADHD should start medication (methylphenidate, atomoxetine, or dexamfetamine) although GPs can continue the medication as part of a shared care approach

School age child/young person with severe ADHD: Offer methylphenidate or atomoxetine (only a healthcare profession who is appropriately qualified and who is expert in ADHD should start medication) as part of a comprehensive plan (include psychological, behavioural, and educational advice/intervention)

Dietary advice: elimination of artificial colouring and additives is not generally recommended for children with ADHD

Adults: Offer methylphenidate as first line treatment (only a healthcare profession who is appropriately qualified and who is expert in ADHD should start medication) unless the patient prefers a psychological approach as part of a comprehensive plan (meet psychological, educational, and/or occupational needs)

(Gilles de la) Tourette syndrome (GTS)

GTS³¹⁵⁶ consists of multiple motor tics³¹⁵⁷ and unprovoked loud utterances that may progress to coprolalia³¹⁵⁸ in 30-60% of cases. Copropraxia may also occur. Prevalence is unknown but is probably more common than is thought³¹⁵⁹. DSM-IV requires an onset before 16 years of age. It affects at least 1/2,000 in the USA and 7 men for every 2 females. A MZ concordance rate of 53% contrasts with a DZ concordance rate of 8%, and risk for first- and second-degree relatives of patients with GTS has been estimated at 3.6% compared to 0.029% in the population at large. Spontaneous cases can occur. Polygenetic inheritance with complex input from the environment appears likely. An autosomal dominant gene with incomplete but high penetrance is possible in some cases. Variants in the SLITRK1 gene have been found in about one percent of GTS cases. It has been surmised that GTS, chronic multiple tics, simple

³¹⁵⁵ Thompson (2008) discusses the controversial aspects of this guidance, e.g. the cost (what other services get cut?), specialisation, licensing (methylphenidate not licensed in UK for adults in 2008), low evidence base (for group therapy), and time required involved, not to mention drugs not mentioned.

³¹⁵⁶ Itard first described this syndrome in 1825. Gilles de la Tourette's description came in 1885. Tourette syndrome may not be a single disorder, e.g. Robertson et al. (2008) observed 5 factors in symptom data from 410 cases: socially inappropriate behaviours and other complex vocal tics; complex motor tics; simple tics; compulsive behaviours; and touching self. Those with co-morbid ADHD had a clearer relationship with the first and third factors, whereas co-morbid OCD was associated with all 4 factors.

³¹⁵⁷ Tics *per se* are not considered pathological unless they cause significant personal distress or social problems. The tics may persist during sleep and become worse with REM sleep. Exacerbation of tics may follow stress, as when someone relaxes after work or school. Factors that may reduce their intensity include sexual arousal or preoccupation with emotionally neutral material.

³¹⁵⁸ Mental coprolalia, where obscenities are thought but not uttered, may be commoner than the overt form. The former may eventually become overt.

³¹⁵⁹ Estimates of lifetime prevalence vary from 0.1 to 1%. Most cases are probably mild and do not present for medical evaluation.

tics, and OCD disorder are expressions of the same gene, that there is a dopamine transmission problem, and that the site of the lesion is in the limbic forebrain structures, especially cingulate gyrus and basal ganglia. However, not all OCD cases are familial or aetiologically related to GTS. (Eapen ea, 2003, p. 968) Broadly distributed cortical systems are likely to be involved in the pathogenesis of GTS. An MRI study (Peterson ea, 2003) found reduced caudate volumes in children and adult GTS cases (possibly a trait abnormality); smaller lenticular volumes may be a marker for comorbid OCD and for persistence of tics into adult life. A smaller corpus callosum might reduce inhibitory input to the prefrontal cortex. (Plessen ea, 2004) fMRI shows increased frontal cortical and caudate activity³¹⁶⁰ when patients attempt to suppress tics and PET reveals an increase in DA receptor and transporter densities plus increased amphetamine-induced release of DA in the putamen. EEG theta activity is associated with more severe cases. Various studies suggested abnormalities of acetylcholine activity, dopamine receptor sensitivity, platelet MAO concentration, and 5-HT metabolism.

Muller ea (2000) found that the mean level of antistreptolysin O and antideoxyribonuclease B titres were significantly higher in children and adults with GTS compared to age-matched controls and to schizophrenic subjects³¹⁶¹.

ADHD symptoms are commonly comorbid with, and often precede, GTS³¹⁶² and both disorders may respond to the alpha-2 agonists clonidine and guanfacine. Obsessive-compulsive symptoms are common in both patients and their relatives. In fact, it has been stated that if OCD and GTS are lumped together there is a good fit for an autosomal dominant model with a penetrance of 0.88 for both sexes. 50% may have hyperkinetic symptoms. Clinical course is one of waxing and waning of multiple motor and vocal tics. One-third has copro- and echophenomena. Copropraxia refers to the occurrence of complex obscene gestures. According to Popper ea (2003, p. 909) up to half these patients are much better or in remission by age 18 years although the opposite (poor outlook with ADHD, depression, learning problems, and conduct disorder) has been reported by Gorman ea. (2010) GTS has emerged during fluvoxamine treatment of an adolescent with OCD.

Treatment includes butyrophenones³¹⁶³, such as haloperidol (Haldol, Serenace), or pimozide; risperidone, olanzapine, or ziprasidone; habit reversal³¹⁶⁴, massed practice³¹⁶⁵ and encouragement of personal responsibility as part of maturation. Psychoeducation is important.

Psychostimulants³¹⁶⁶, often used for attentional and hyperactivity states, may precipitate motor or vocal tics that may persist after discontinuing the medication. It is suggested that they should therefore only be employed with extreme caution if there is a family history of tics or GTS. Some authors, however, believe that stimulant-induced tic exacerbation is unlikely. (Popper ea, 2003, p. 911; Huffman & Stern, 2008, p. 719) Methylphenidate may be associated with psychotic symptoms.³¹⁶⁷ Hyperkinesia may respond to TCAs.

Most individuals with tics lead reasonably normal lives, and the tics tend to improve during the teens. (Chowdhury & Heyman, 2004) Oesterheld ea (2003, p. 360) caution against stimulant abuse among the relatives of children receiving treatment with such drugs.

Deep brain stimulation (electrodes placed in midline thalamus, nucleus accumbens, or globus pallidus interna) has been used for severe, intractable tics. (e.g. Ackermans ea, 2008) Other treatment approaches include vocal cord injections of botulinum toxin (Porta ea, 2004) for vocal tics and coprolalia. The latter produced hypophonia in 80% of cases.

³¹⁶⁰ With decreased activity of thalamus, globus pallidus, and putamen.

³¹⁶¹ See *PANDAS* - paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.

³¹⁶² According to a nested case study of children assessed for GTS at specialised clinic (Pringsheim ea, 2009) children with this syndrome are more likely to have comorbid ADHD if their birth weight was low and if their mothers smoked.

³¹⁶³ Chemically related to pethidine.

³¹⁶⁴ Patient learns to recognise (with help from the therapist) and describe tics as well as recognising recurrences and what circumstances may precipitate them. He (or she) re-enacts tics into a mirror. The patient uses competing responses (such as isometric contraction of opposing musculature) when the urge to tic occurs.

³¹⁶⁵ Each tic is repeated voluntarily until it is extinguished.

³¹⁶⁶ E.g. dextroamphetamine, methylphenidate and pemoline – pemoline was withdrawn in UK because of fatal hepatotoxicity, sometimes after many months of use.

³¹⁶⁷ 6% of children in retrospective chart review. (Cherland & Fitzpatrick, 1999)

Kluver-Bucy syndrome

Kluver (or Klüver) and Bucy described this in 1939. Although it has since been diagnosed in man, it was originally described in monkeys following bilateral temporal lobe destruction. Features include the examination of all available objects with the mouth, licking and biting, hypermetamorphosis (nothing ignored and constant exploration), always exploring, placidity, hyperphagia, and hypersexuality (including homosexuality and sexual intercourse with other species). There is psychic blindness (responds in a similar manner to an orange as to a charging bull - able to see but he is unable to meaningfully discriminate between objects). Parts of this syndrome are commonly present in (usually late) AD and are associated with greater temporal lobe atrophy (reduced counts of large neurones in parahippocampal gyrus and parietal neocortex – cortical inhibition with relatively intact subcortical structures?). Again, parts of the syndrome may occur early in the course of frontotemporal dementia.

Diogenes or Plyushkin's syndrome³¹⁶⁸

Diogenes syndrome is named for Diogenes of Sinope, (Wrigley & Cooney, 1992; O'Shea & Falvey, 1997; Cooney, 1997) a Greek cynic philosopher³¹⁶⁹. Clark coined the term in 1975 to describe gross self-neglect in old age and Post called it 'senile recluse'. Plyushkin was a character in Gogol's novel 'Dead Souls'. The syndrome is found about equally in men and women. Affected persons often refuse help from professionals and they collect all sorts of rubbish (*syllogomania*). About 50% have a formal psychiatric illness at the time of examination, but far fewer have been admitted to psychiatric care. In fact, such patients often flatly refuse to be helped. (Hurley ea, 2000) The most common psychiatric diagnoses are Alzheimer's disease (AD), chronic paranoid schizophrenia, chronic alcoholism, and bipolar affective disorder. The death of a close relative may be a precipitating factor in those with no psychiatric illness. There is a high physical morbidity and mortality. Some cases may have frontal lobe dysfunction. (Sikdar, 1999) Community studies suggest a somewhat different profile for people living in squalor: somewhat younger males of lower social class who are mentally ill and older people who are physically ill. (Halliday ea, 2000) Cases of married couples with so-called 'Diogenes à deux' have been reported. (e.g. Cole ea, 1992) Diogenes syndrome represents a dilemma for psychiatry and for society. Do we let patients live and squalor in case we infringe human rights³¹⁷⁰ ('rotting with their rights on')? Do we insist on doing something because of the danger of infectious disease? The answer is easier when the patient is obviously psychotic.

Sick building syndrome (SBS)

Various uncomfortable or even disabling symptoms and illnesses have been attributed to non-industrial indoor environments, especially schools and (tall) office buildings. (O'Shea, 2002a) Objective physiological abnormalities are uncommon.

Common symptoms in SBS

Irritation of throat and eye
Headache
Fatigue
Diminished concentration
Dyspnoea, wheeze, irritating cough
Skin rash, itch, and dryness

³¹⁶⁸ Other names include *Augean Stables syndrome* and *social breakdown of the elderly syndrome*. The stables in Greek myth belonged to Augeas (Augeias) who was king of Elis. The stables, unclean and housing many cattle, were cleaned by Heracles (Hercules) who achieved his task in a single day by rerouting rivers.

³¹⁶⁹ Diogenes (c. 412 or 404-323 BC) was a native of Sinope, now Sinop in Turkey. A beggar who admired poverty and decried human achievements, he lived in an Athenian tub and ate onions.

³¹⁷⁰ In the UK the provisions of *The National Assistance Act 1948, section 47* are rarely used.

Increased or abnormal odour perception
Visual disturbances

Suggested causes

Air contaminants, e.g. photocopiers, cleaning agents, paints/resins, bacteria
Ventilation

Work organisation – job satisfaction, stress, social factors

Host factors – commoner in females, atopy, airway hyperactivity, and pre-existing disease

“Mass psychogenic illness” – many people within close proximity to one another (e.g. the same building) develop non-specific symptoms of illness through a process of suggestion

Some trigger may start the condition, such as a disagreeable odour or an unexplained noise. The key to diagnosis is the almost simultaneous development of roughly the same symptoms by a number of people inhabiting the same building. SBS must be distinguished from a non-random collection, e.g. anxious patients in a specialist unit; toxic emissions, e.g. lead, mercury, coal dust; infectious diseases, e.g. influenza, tuberculosis; Gulf War syndrome; fibromyalgia (FMY); chronic fatigue syndrome (CFS); and multiple chemical sensitivity (MCS).

‘Multiple chemical sensitivity’ (MCS) patients often meet diagnostic criteria for the other polysymptomatic syndromes just mentioned viz.: - FMY, CFS, and SBS, and many MCS patients may attribute their symptoms to the toxic environment of a building. Interestingly, many Persian Gulf War veterans who blamed symptoms on toxic exposures have attracted a diagnosis of MCS. Gulf War syndrome (cognitive difficulties, fibromyalgia, depression, anxiety, respiratory problems and chronic fatigue) is not unique to that conflict. Ismail *et al.* (2002) felt that psychiatric disorders did not fully explain self reports of ill health in people with Gulf War syndrome but there is no evidence that it is caused by neurological problems. (Bryant, 2008)

Since the syndrome is poorly understood it is impossible to be dogmatic. One can treat the patient and/or the building. Examples of the latter include improving ventilation systems and reducing any contaminant exposure. There is no evidence for ill effects from fluorescent lighting. The patient may need counselling, medication, career guidance/change/retirement – or whatever is appropriate, keeping in mind the necessity of non-reinforcement. Permanent sequelae appear to be rare.

Humidifier fever is due to contamination of humidifying systems in air conditioners in factories and office blocks with bacteria, thermoactinomyces or amoebae. It may present with the symptoms of extrinsic allergic alveolitis: fever, cough, dyspnoea etc. Management involves sterilising the water used in humidifying plants. Legionnaire’s disease results from contaminated air-conditioning systems.

Whiplash

Whiplash neck injury is the most common injury sustained in road traffic accidents (RTAs). The head is suddenly and unexpectedly jolted whilst the head moves freely, as when one car hits another from behind. The neck is suddenly extended, flexed, or rotated excessively. Soft tissue damage occurs in the cervical area. Claims for persistent symptoms make up a large percentage of all personal injury claims. The history of whiplash is one of acrimony! Are these people physically injured, psychologically traumatised, or ‘on the make’? In the Karlsborg *et al.* (1997) series of 39 patients there are 6 cases of whiplash in females for every 4 cases in males. Mayou and Bryant, (2002) looked at consecutive post-RTA hospital emergency attenders. Moderate to severe pain was reported by 27% of whiplash sufferers at 1 year and by slightly more (30%) at 3 years. Psychiatric sequelae (PTSD, travel anxiety, anxiety, depression) were common but no more so than with other types of injury. Accident-associated and post-accident psychosocial variables predicted pain severity at 12 months. Whilst whiplash was especially associated with compensation seeking, the authors suggested that this was explained by ‘the high proportion of innocent victims, the physical symptoms and the ease of legal definition’. This research was based on case notes and self-reports at follow-up, and response rates declined over the follow-up period. Like Cassidy *et al.* (2000), Thomas (2002) emphasises the potential of litigation (as distinct from no fault compensation) to worsen and prolong suffering and reduce functioning.

Out of body experiences

Out of body experiences are mainly associated with epileptic seizures and migraine. They affect about 10% of the population.(Blanke ea, 2004) They are usually spontaneous, short-lived, and extremely infrequent. However, they may be repetitive. Self or the centre of awareness of oneself is experienced outside of the body. The experience includes the experience of seeing the world (incl. the body) from a position above the body. The underlying pathology is within the temporo-parietal junction. Electrical stimulation of this part of the brain can evoke illusions of elevation, rotation, lightness, flying, and limb shortening or movement.(Blanke ea, 2002)

Dupuytren's contracture

This is a common, usually painless, often bilateral and familial, slowly progressive fibro-proliferation of the superficial palmar fascia leading to pitting and thickening of the skin of the palm with firm, painless nodule fixed to skin and deep structures.(Townley ea, 2006) A cord forms eventually and contracts flexing the finger/s so that they catch in pockets or stick in an eye when washing. Fibrosis may also occur on the soles of the feet (plantar fibromatosis), knuckle pads, and penis (Peyronie's disease). It typically affects older European males, although females by no means immune.

Factors associated with Dupuytren's contracture

Alcohol
Smoking
Anticonvulsant drugs and epilepsy (controversial)
Diabetes mellitus³¹⁷¹
Manual labour/trauma (vibration: disputed in the literature)
Hypercholesterolaemia
HIV infection

Treatment approaches include (injected) collagenase (from *Clostridium histolyticum*: Hurst ea, 2009), fasciectomy, and, for recurrent/aggressive cases, dermofasciectomy. However, many cases do not progress to contracture.

Trace elements

Trace elements occur in living tissues in extremely small quantities. Some are essential for life. The association between trace elements and mental illness is circumstantial at present.

Aluminium: This has been incriminated in associated dialysis encephalopathy³¹⁷². Reducing the amount of aluminium in the water for dialysis prevents this encephalopathy. Contamination of water by huge quantities of aluminium³¹⁷³ may have led to some brain damage. Exposure in the workplace (welders, etc) may lead to tremor, impaired balance, reduced recall memory, and slowing of cognition. Contamination with other substances, such as manganese, must be considered.

Cobalt: Cobalt is found at the centre of the vitamin B12 molecule. Cyanocobalmin (B12) deficiency (most often due to pernicious anaemia with antibodies against parietal cells and intrinsic factor) may cause anaemia, eye problems, spinal cord degeneration³¹⁷⁴, neurasthenia, depression, paranoid psychosis with

³¹⁷¹ May have nodules or skin and knuckle pad thickening.

³¹⁷² Aluminium is also found in Alzheimer lesions.

³¹⁷³ E.g. in Cornwall in 1988.

³¹⁷⁴ Deficiency of B12 may cause demyelination of centrum semiovale as well as the posterior columns and lateral corticospinal tracts.

hallucinations³¹⁷⁵, and delirium or (rarely) dementia. The serum B12 may be low. However, some cases of B12 deficiency, especially older subjects, may have normal B12 levels but elevated methylmalonic acid and homocysteine levels³¹⁷⁶. Always think of B12 deficiency in vegans or in the patient with reduced peripheral vibration sense. In cobalmin deficiency, the EEG is slowed with excess theta waves throughout. Neuroimaging may show involvement of periventricular white matter. B12 deficiency may follow nitrous oxide inhalation.

Copper: This is important in many enzymes and proteins. Hepatolenticular degeneration³¹⁷⁷ is an uncommon inborn error of metabolism of autosomal recessive inheritance (mutations or deletions of ATP7B protein encoded at 13q14.3-q21.1) wherein copper is deposited in various organs, especially the brain and liver. Untreated cases die in adolescence or early adulthood. Successful treatment is now available with chelating agents such as penicillamine. The commonest psychiatric complications are non-specific affective or behaviour disorders, but schizophreniform or bipolar psychoses can also occur. Psychiatric manifestations may precede physical signs.

Menkes' kinky hair syndrome is a rare sex-linked recessive disorder associated with copper malabsorption. The gene ATP7A encodes a copper-transporter ATPase. Infants fail to grow, have intellectually disability, brittle hair, anaemia, neutropaenia, and bone lesions.

Manganese: Manganese is an essential trace element and is plentiful in the environment. It acts as a co-factor of numerous enzymes. It is absorbed via the GIT but in toxic cases the main route into the body is by inhalation. Manganese in toxic doses damages DNA, probably by producing excess free radicals.

Manganese is found in steel castings, ore refineries, dry battery manufacture, bleaching, electro-welding, a fungicide (MANEB), and brick working. Use of an organo-manganese compound (MMT) as an antiknock agent in petrol is not known to humans as yet. An MRI contrast agent (mangafodipir trisodium) may lead to contamination. A high manganese level has been associated with psychosis ('manganese madness'³¹⁷⁸) and Parkinsonism³¹⁷⁹, e.g. in the mining areas of Chile. Manganese is chelated by the phenothiazines. Nocturnal leg cramps are common in manganese poisoning. There is a tentative association with dementia. Some cases may walk with their heels in the air and with their elbows flexed (cock-walk). The patient must be removed from sources of contamination although improvement is not guaranteed. L-DOPA is much less effective than in Parkinson's disease (paralysis agitans).

Manganese deficiency may occur during parenteral feeding.

Lead: Tetraethyl lead in petrol, for example, may cause an encephalopathy. This may present in the adult with delirium and seizures, often with associated hypertension. Chronic encephalopathy is characterised by headache, trembling, impaired memory and concentration, poor hearing, and episodic hemianopia and aphasia. Children are particularly badly affected and may develop coma, pareses, papilloedema, meningism, and compression of medullary centres, and those who survive may be brain damaged or blind. EDTA may be given parenterally. Alternatively, the oral chelating agent meso-2,3-dimercaptosuccinic acid may be used.

Lead poisoning (plumbism)

Sources of lead range from lead toys (common in the author's childhood), retained bullets (especially in a joint space or a pseudocyst), and illegal whiskey (use of old car radiator)

Lethargy

Blue line on gum margins (lead sulphide deposition)

Lead lines on x-rays of long bones in children

Abdominal discomfort or pain, vomiting, constipation

³¹⁷⁵ 'megaloblastic madness'. (Smith, 1960)

³¹⁷⁶ **Methylmalonate** and **homocysteine** are substrates of cobalmin-dependent reactions. They may be more sensitive indicators of tissue B12 deficiency than B12 levels themselves. Folic acid and B12 act as co-factors in re-methylation of homocysteine to methionine, deficiency of either vitamin causing increased homocysteine levels. Homocysteine increases neuronal excitotoxicity by stimulating NMDA receptors. Oxidative stress is increased leading to damage to DNA and apoptosis. Kim et al (2008) suggest that low B12, low folate and raised homocysteine levels may increase risk for late-life depression.

³¹⁷⁷ Kinnier Wilson described hepatolenticular degeneration (Wilson's disease) in 1912.

³¹⁷⁸ Labile moods, inappropriate laughter, aggression, hallucinations, and Parkinsonism.

³¹⁷⁹ Manganese-induced Parkinsonism is associated with damage to the pallidum and striatum whereas the substantia nigra pars compacta bears the brunt in paralysis agitans. Uptake of fluorodopa is normal in manganese-induced Parkinsonism but reduced in paralysis agitans.

Sideroblastic anaemia, mild haemolysis, punctate basophilia³¹⁸⁰
 Encephalopathy (delirium, seizures, coma)
 Peripheral motor neuropathy (foot drop)

Rubidium: Rubidium³¹⁸¹ causes euphoria. Hopes of replacing lithium with rubidium were upset by suggestions of neurotoxicity.

Vanadium³¹⁸²: It is thought that vanadate, the pentavalent ion, inhibits Na-K-ATPase and hence the Na⁺ pump. Vitamin C converts this to the tetravalent ion, vanadyl (methylene blue has the same effect). It has been suggested that vanadium, as vanadate, can cause depression.

Selenium: This is commonly found in skin applications and can cause tremor and loss of appetite if absorbed transcutaneously over a long period of time. Depletion might be a cause of depression and other negative mood states, such as anxiety, confusion and hostility.

Zinc: Zinc is involved in RNA synthesis and RNA is important in memory functions. Low zinc levels have been suggested as a possible cause of dementia. Well recognised symptoms of zinc deficiency include depression and perverted taste and smell. Low zinc levels are associated with poor nutrition and high phytate levels in bread. Zinc deficiency may also occur in malabsorption states, regional enteritis, hepatic failure, kidney disease, certain drugs (e.g. histidine), and diabetes mellitus. Treatment is with zinc sulphate. High zinc levels have been found in multiple sclerosis and in neural tube defects. Zinc (as acetate or sulphate) is used as a copper depleting agent in Wilson's disease. Zinc supplements given to pregnant poor Bangladeshi women did not confer benefit on their infants' mental development (Hamadani et al, 2002) although it does seem to reduce mortality in infants from infectious diseases.

Electrolytes and acid-base balance disorders

Hyponatraemia: symptoms include nausea, vomiting, abdominal pain, anorexia, weakness, dizziness, headache, blurring of vision, sweating, malaise, lassitude, apathy, muscle cramps and twitching, delirium, coma, and hypotension. Various psychotropics (carbamazepine, oxcarbazepine, neuroleptics, TCAs, SSRIs, etc), diuretics, hypoadrenalism, various kidney diseases, and myxoedema may cause hyponatraemia. Patients with psychogenic polydipsia and those with eating disorders who drink water to produce a full feeling are at risk of hyponatraemia. Burn patients, those who sweat excessively in tropical climates, people with GIT diseases (e.g. vomiting, diarrhoea, tube drainage, fistula, etc),

Hyponatraemia in cancer patients can be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to paraneoplastic syndrome³¹⁸³. Low sodium (< 125 mmol/L) or a rapid fall in sodium level can lead to agitated delirium whereas more chronic hyponatraemia may be associated with poor attention and falls in older patients. Central pontine myelinolysis is a rare disorder of cerebral white matter and has multiple causes; rapid correction of hyponatraemia (common in beer drinkers, especially when replacing vomited fluids with hypotonic fluids) may be a factor in the aetiology (although not invariably so), the condition presenting a day to a week later.

A low sodium diet may be useful in reducing blood pressure in patients with multiple risk factors for the metabolic syndrome.

Hypernatraemia: either too much water is lost or too little water is taken in; older people are at highest risk; there can be xerostomia, weight loss, grey complexion, lethargy, confusional state/delirium, and muscular hypertonicity; seizures and central pontine myelinolysis may follow over vigorous rehydration; shrinking of the brain may cause bleeding from veins; cerebral sinus thrombosis is a known complication; hypernatraemia may occur with anabolic steroid abuse or in diabetes insipidus.

Hypokalaemia: this may occur in hepatic cirrhosis, metabolic alkalosis, vomiting, or laxative/diuretic/anabolic steroid abuse; there is reduced intake of potassium, a movement of potassium into cells, or excess potassium loss. Clinical findings include lethargy, apathy, anorexia, constipation,

³¹⁸⁰ Punctate basophilia: round, blue particles in red cells represent RNA aggregates in immature red cells.

³¹⁸¹ The bromide of rubidium was in common use in the 19th century for a variety of disorders, e.g. epilepsy.

³¹⁸² Scandinavian goddess Vanadis. Vanadium received wide usage for a variety of problems in the 19th century (e.g. neurasthenia).

³¹⁸³ SIADH may be due to small cell carcinoma, mesothelioma, pancreatic or duodenal cancer, brain neoplasm, leukaemia, pulmonary infection, carbamazepine, tranylcypromine, TCAs, SSRIs, or phenothiazines and other antipsychotic drugs.

depression, anxiety, delirium (rarely), paralytic ileus, proximal muscle weakness/myalgia, and EEG changes (flat/inverted T waves, prominent U waves, depressed ST segment, and prolongation of QT interval). When giving potassium with IV fluids normal saline is better than dextrose as the latter increases intracellular shifts in potassium by insulin.

Hyperkalaemia: this is chiefly a problem with kidney failure; clinical features include fatigue, muscle weakness (flaccidity in extreme cases), lethargy, confusion and cardiac arrhythmias (bradycardia due to heart block, ventricular fibrillation/asystole). The classic ECG progression is from normal to tented T waves, small P waves and widened QRS complex, to 'sine wave' pattern, to cardiac arrest.

Calcium: High serum calcium (hyperparathyroidism, cancer) causes depression, anxiety, and delirium; low serum calcium (diet low in calcium or vitamin D, hypoparathyroidism, rhabdomyolysis, kidney/liver disease, anticonvulsant drugs, thyroid/parathyroid surgery) can cause cramps, tetany, and seizures.

Hypophosphataemia: phosphate may move into cells during management of diabetic ketoacidosis or alcoholism; it is also encountered during refeeding of people who have been starving; clinical features may include anxiety, irritability, delirium, ataxia, slurred speech, breathing irregularities, weakness of extraocular muscles, paralysis, areflexia, myoclonus, and paraesthesiae (in hands and feet). Weakness of the diaphragm may make it difficult to stop artificial ventilation. Wernicke's syndrome or Guillain-Barré syndrome may be mimicked in hypophosphataemia.

Magnesium: This is important in neuromuscular transmission. Magnesium reduces neuronal excitability in delirium tremens. Any patient who has fluid and other electrolyte imbalance and who unexpectedly develops neurological problems should have magnesium levels checked.

Hypomagnesaemia is common and is found in association with alcoholism, medication (e.g. loop diuretics, cyclosporine, cisplatin, aminoglycosides) renal, endocrine and GIT disorders. Severe hypomagnesaemia leads to functional underactivity of the parathyroid glands which responds to magnesium replacement. A low magnesium level is found with infantile seizures. Magnesium and calcium concentrations are lowered by neuroleptics. Tetany is a common feature (as with hypocalcaemia). Other potential manifestations include irritability, depression, vertigo, ataxia, muscular weakness/fasciculation, seizures, myoclonus, choreoathetoid movements, and focal symptoms and signs such as dysphasia and hemiparesis. The ECG may show prolongation of the QT interval, T waves that are flat and broad, and there may be shortened ST segments. Affections of consciousness vary from slight confusion via delirium to coma. Treatment is with magnesium sulphate.

Hypermagnesaemia is uncommon (e.g. in renal failure, excess magnesium in dialysate during haemodialysis, or over indulgence in antacids [magnesium trisilicate] or laxatives [magnesium sulphate]) and causes a general depression of the CNS.

Acidosis³¹⁸⁴: reduced level of consciousness and tachypnoea. Examples of drugs that may lead to metabolic acidosis are ethanol, ethylene glycol, diethylene glycol, methyl alcohol, TCAs, topiramate, metformin, calcium channel blocking drugs, iron, paracetamol (acetaminophen), cocaine, CO, and cyanide (hydrogen cyanide = prussic acid).

Alkalosis: apathy, disorientation, delirium, tetany and paraesthesiae.

Endocrinopathies

Due to earlier diagnosis, depression and anxiety are the commonest neuropsychiatric phenomena encountered in this group of disorders. More obviously organic presentations, such as delirium and dementia are associated with longer duration of the endocrinopathies.

Adrenals: Conn's syndrome is associated with severe weakness due to hypokalaemia. In Cushing's disease there are weakness, agitation and depression. The depression may relate to ACTH rather than to glucocorticoids, which might explain the tendency of exogenous steroids to cause euphoria or elation. Hippocampal volume reduction and elevated cortisol levels have been reported in Cushing's disease that are reverse with treatment. (Starkman et al, 1999) Addison's disease causes apathy, depression and loss of libido. A paranoid illness may accompany Cushing's disease and delirium occurs in Addisonian crises.

³¹⁸⁴ Arterial pH is held in the range 7.35-7.45. This is the job of buffering mechanisms, the lungs, and the kidneys.

Adrenal medulla: Phaeochromocytoma (90% in adrenal, 10% in sympathetic chain), which may be episodic or continuous, can be mistaken for anxiety neurosis, hysteria or panic states. TCAs and SSRIs may unmask silent cases and MAOIs may be disastrous. Before and during surgery it is essential to use complete alpha-blockade *followed by*³¹⁸⁵ complete beta-blockade, i.e. phenoxybenzamine first and then add propranolol. This combination is continued if surgery proves to be impossible.

Features of phaeochromocytoma

Apprehensiveness
 Headache, dizziness, tremor
 Hyperhidrosis, pallor or blushing
 Dyspnoea, palpitations, central chest pain
 Nausea and vomiting
 Glycosuria
 Arterial hypertension
 Various complications, e.g. myocardial infarction, CVA, papilloedema, haemorrhagic retinitis, convulsions, ventricular fibrillation, and diabetes mellitus
 At least annual catecholamine excretion assessments are performed post-operatively as there is at least a 10% recurrence rate

Diagnosis

24 hour urine collection – metanephrines and VMA
 Metanephrines are the most sensitive
 Urinary VMA can be increased by dietary vanillin (e.g. vanilla extract, citrus foods, bananas, nuts, and coffee)
 MRI and (for extra-adrenal tumours) [131I]metaiodobenzylguanidine scan

Factitious phaeochromocytoma

E.g. vanilla extract ingestion

Thyroid: Only 20% of T₃, the active thyroid hormone, is readily produced in the thyroid gland, and the cells of many tissues de-iodinate T₄ to T₃. The liver is a major 'exporter' of T₃. Thyrotoxicosis must be distinguished from anxiety neurosis, and myxoedema³¹⁸⁶ from melancholia. There were a number of reports of Graves' disease developing following severe stress during the 1914-18 war. The first description of a treatable dementia was probably a case of hypothyroidism, although unconnected hypothyroidism in dementia is commoner than causative hypothyroidism.

Some chemical causes of myxoedema

Lithium
 Carbimazole
 Sodium aminosalicylate
 Phenylbutazone
 Resorcinol ointment

The features are puffy, especially in areas of loose tissue (e.g. under the eyes), there is a non-pitting swelling of the face, limbs and above the clavicles, and the skin is dry. Other features of the condition are lifeless, thinned hair; slow, coarse and monotonous speech; apathetic appearance; angina; bradycardia; anorexia; poor concentration and recent memory; irritability; generalised aches and pains; and dulling of the special senses.

'Polar T₃ syndrome'

Described in persons wintering in Antarctica

³¹⁸⁵ If this sequence is not followed extreme hypertension develops. Sodium nitroprusside is used for sudden extreme hypertension.

³¹⁸⁶ Richard Asher described 'myxoedematous madness' in 1949. There is no consistent picture. It can resemble paranoid schizophrenia, dementia, or depression.

Raised TSH, decreases in total and free T3 and free T4, although levels are still usually within normal limits

Mood changes may occur

Parathyroids: Weakness, depression, delirium, dementia, 'hysteria' and anxiety.

Hypopituitarism: Weakness, depression, delusions, delirium and dementia.

Vitamins in relation to psychiatry³¹⁸⁷

Studies during the 1980s that were conducted among psychiatric and institutional populations found widespread vitamin B deficiency. B group deficiency was strongly linked to endogenous depression and alcoholism. The main drugs associated with avitaminosis were most psychotropic drugs, anticonvulsants, the anovulant pill, antileukaemic agents, antibiotics, and isoniazid. 10-30% of psychiatric patients had folate deficiency (vitamin Bc). According to Carney (1992) depression is the main psychiatric manifestation of folate deficiency. This receives support from work by Sachdev ea.(2005)

Thiamine (B1) deficiency

Failure to convert pyruvate (from glycolysis) to acetyl coenzyme A and, in the citric acid cycle, alpha-ketoglutarate to succinyl coenzyme A

Famine, poverty, alcoholism, malignancy, Hyperemesis gravidarum, AIDS, dialysis, bariatric surgery (Foster ea, 2005)

Commonest form – mixed cerebro-neuropathic-cardiac

Wernicke-Korsakoff syndrome (WKS) including iatrogenic (glucose given in B1 deficiency)

Beriberi - cardiac³¹⁸⁸ (wet) and neurological³¹⁸⁹ (dry) forms +/- WKS³¹⁹⁰

Pyridoxine (B6) deficiency³¹⁹¹

Infantile seizures

Neuropathy

Lethargy

B6-responsive sideroblastic anaemia

MAOIs may cause B6 deficiency, e.g. weakness and paraesthesia

Premenstrual symptoms (?)³¹⁹²

Anovulant-related depression (?)

Nicotinic acid (niacin) deficiency (see discussion of pellagra)

Low serum niacin and 24-hour urinary niacin metabolites

Acute deficiency may lead to an encephalopathic state

Pellagra in subacute cases, preceded by 'neurasthenia'

Pellagra is a rare complication of carcinoid syndrome³¹⁹³

Pellagra may be seen in Hartnup disease³¹⁹⁴

Pantothenic acid deficiency

Sensory neuropathy, 'burning feet' (?)

³¹⁸⁷ Christiaan Eijkman proposed the existence of essential factors in food as a result of his research on beriberi. Casimir Funk used the term 'vitamin' in 1912.

³¹⁸⁸ High output failure with tachycardia, dilated peripheral vasculature, and oedema.

³¹⁸⁹ Peripheral neuropathy (mixed).

³¹⁹⁰ WKS may require a genetically determined transketolase abnormality.

³¹⁹¹ Pyridoxal phosphate is a cofactor in amino acid metabolism. Deficiency may be due to drugs such as isoniazid, penicillamine and hydralazine.

³¹⁹² Do not exceed 10 mg/day. Excessive, prolonged use may lead to a polyneuropathy.

³¹⁹³ A majority of body tryptophan is broken down via a minor pathway.

³¹⁹⁴ Excess excretion of tryptophan via the kidneys and reduced gut absorption of tryptophan.

Decreased vitamin D may be associated with geriatric depression.(Hoogendijk ea, 2008) Vitamin D deficiency is very common in long-stay units where residents do not get outside³¹⁹⁵.(Tiangga ea, 2008) The chief source of vitamin D is UVB. Other sources are fish, eggs, dairy products, and fortified cereals or margarine. Lack of sunlight³¹⁹⁶, malabsorption, liver/kidney dysfunction, phenytoin, carbamazepine, dark skin, and obesity, have been associated with vitamin D deficiency. Alcohol, anticonvulsants, oral contraceptives, methotrexate, pyrimethamine, triamterine, trimethoprim, and sulphasalazine can reduce folate levels, whereas nicotine, H2-blocking drugs, oral contraceptives, zidovudine, metformin, and cholestyramine may lead to B12 deficiency³¹⁹⁷. The effectiveness of phenobarbital, phenytoin, and methotrexate may be reduced by folate.(Reynolds, 2002) There were exaggerated claims in the UK that healthy children would become more intelligent if they consumed extra vitamins.(Dyer, 1992) Also, hypothyroidism and deficiencies of B12 and folate are usually coincidental findings in dementia rather than aetiological factors. Folate, B6 and B12 decrease homocysteine levels, an effect that might reduce the risk for Alzheimer's disease.(Luchsinger ea, 2007) However, Aisen ea (2008) found that high-dose folate, B6 and B12 failed to slow cognitive decline in cases of mild-to-moderate Alzheimer's disease (MMS scores 14-26 inclusive) who had normal folate, B12, and homocysteine levels. Exposure to folic acid antagonists (e.g. anticonvulsants and trimethoprim) during the first trimester of pregnancy increase the risk for congenital defects, especially those affecting the neural tube.(Matok, 2009) Red cell folate is more informative than serum folate about tissue levels over time, whereas serum levels are more immediately affected by changes in diet. Alpha-tocopherol (vitamin E) deficiency may be involved in neurodegeneration.

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³¹⁹⁵ Treat with daily supplements of calcium and ergocalciferol.

³¹⁹⁶ Sunlight may be blocked by staying indoors, sunscreens, or clothing.(Pearce & Cheetham, 2010)

³¹⁹⁷ 'Megaloblastic madness' (delirium) = hallucinations, paranoid thinking, and cognitive decline.

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Agnosia

Inability to recognise and interpret the significance of sensory perceptions³¹⁹⁸; can take many forms.

Anosognosia, denial of illness (a form of hemi-inattention; a left hemiparesis is not acknowledged due to a non-dominant parietal lobe lesion³¹⁹⁹; this causes management problems because the patient does not see why he needs assistance)

The term **disconnection syndrome**³²⁰⁰ suggests an interruption of communication between brain regions in sensory inattention and neglect following a stroke.³²⁰¹

Autopagnosia, denial of body part, e.g. finger³²⁰²

Asomatagnosia, denial of ownership of a paretic limb, sometimes attributing ownership to another person, with a right-sided lesion.³²⁰³

Visual agnosia, inability to recognise objects visually³²⁰⁴, mostly attributable to bilateral (less often right-sided only) medial occipitotemporal lesions.

Auditory agnosia, inability to recognise sounds, everything from a telephone ringing to speech – all is simply noise (usually bitemporal lesions).

Astereognosis, inability to recognise objects by touch.

Topognosia, inability to recognise an object placed on the skin.

Agrophagnosia (agraphaesthesia), inability to recognise numbers or letters written on skin. **Prosopagnosia**, inability to recognise familiar faces.³²⁰⁵

Simultagnosia: inability to recognise more than one element at a time of a visual scene (right temporo-occipital lesion); and, more controversially from the definitional point of view.

Topographagnosia, where patients cannot recognise items like buildings³²⁰⁶.

Alternating sequences: draw a short sequence of alternating squares and triangles and ask patient with frontal lobe pathology to copy the sequence and then continue the pattern; the patient will repeat shapes instead of alternating them.

Aphasia

Aphasia: Broca's area³²⁰⁷ is just below the motor area for the right hand and face. Wernicke's area³²⁰⁸ is in the posterior part of the dominant superior temporal gyrus. The two areas (in most people in the left hemisphere) are joined by the arcuate fasciculus that passes through the angular gyrus. Cerebral dominance is not well established in very young children.

Dysphasia (the complete form being aphasia) is an organic impairment of language and communication.

Receptive (sensory, fluent, jargon) aphasia - patient hears but cannot understand (lesion in Wernicke's area³²⁰⁹; speech is fluid and spontaneous but incoherent and nonsensical) and is unaware of the problem; motor function is normal

Expressive (motor, non-fluent) aphasia (lesion in Broca's area) - patient understands others but cannot express himself normally: speech is halting, laborious, inaccurate, inarticulate, telegraphic, sparse, or even absent - in the lesser, *dysphasic* form the appropriate words cannot be found despite knowing what it is one wants to say; right hemiplegia common

Global (total) aphasia - combination of (a) and (b) - speech is non-fluent and the patient shows by his emotional reaction that he is unaware that there is a problem; may be mute; variable right hemiplegia

Conduction aphasia - similar to sensory/fluent aphasia but with understanding and awareness of deficits, the latter leading to frustration; there is selective impairment of repetition

Nominal dysphasia (anomia, amnesic aphasia) - inability to find words or name objects that patient should know (e.g. a pen or a watch) - tested for in detail by asking the patient to (1) name 12 familiar (e.g. a cup) and unfamiliar (e.g. examination couch; teeth of a comb) objects while he handles each in turn, and (2) name as many members of stated categories (e.g. flowers or animals) as can be recalled

Patients with Broca's dysphasia are frustrated: **emotional speech** is found in such patients: they may utter words or sentences when experiencing great emotion that they would otherwise be unable to produce. The acute onset of abnormal speech in a middle-aged person is almost always diagnostic of a fluent aphasia. (Geschwind, 1971) **Fluent dysphasia** may be misdiagnosed because many

³¹⁹⁸ *Gnosis*: ability to recognise objects, faces, sounds, or body parts.

³¹⁹⁹ Other authorities point to the right frontal cortex.

³²⁰⁰ Term coined by Norman Geschwind in 1965.

³²⁰¹ Neglect can be visual, wherein a clock is drawn with figures bunched to one side, or motor, as when only one hand is used to carry out a task without any neurological finding by way of explanation. The negation of hemi-neglect by the application of transcranial magnetic stimulation to the intact hemisphere (Oliveri et al, 1999) suggests that it is interhemispheric imbalance rather than damage to the other hemisphere that leads to hemi-neglect.

³²⁰² Tests for finger agnosia: recognise/name individual fingers; name finger being touched whilst patient keeps eyes closed.

³²⁰³ Usually parietal but can be internal capsule, striatum, or thalamus.

³²⁰⁴ In contrast, *deep dyslexia* refers to an ability to read the sense of a word but a word with similar meaning is substituted consciously, e.g. 'terminal' for 'ending' – a form of adaptation to neural damage.

³²⁰⁵ Same areas are affected as in visual agnosia; may occur as part of simple partial seizure, when it is of brief duration.

³²⁰⁶ Alternatively defined as a loss of sense of direction – see 'geographical disorientation'.

³²⁰⁷ Posterior part of inferior frontal gyrus of dominant hemisphere, i.e. Brodmann's areas 44 and 45.

³²⁰⁸ Discovered in 1874 by Carl Wernicke (1848-1905): worked with Heinrich Neumann (1814-1884) in Breslau and succeeded him as professor of psychiatry and neurology in 1885; professor of psychiatry in Halle from 1904. Also known for idea of loosened continuity of nerve fibres in psychosis ('sejunction' theory).

³²⁰⁹ Can be due to diffuse disorders like Alzheimer's disease but vascular causes are more common, e.g. vascular dementia due to CVA affecting temporal or parietal lobes.

doctors are unaware of the frequency of aphasia without a hemiplegia. The patient may be mislabelled as ‘psychotic’ or ‘confused’, especially when there is a rapid outpouring of abnormal speech. In practice, the differential diagnosis is not always straightforward.

Nominal dysphasia, unlike primary motor aphasia, may be commoner in diffuse rather than focal brain dysfunction (e.g. Alzheimer’s disease), and it is often accompanied by **acalculia** (inability to do simple arithmetical calculations; tested for by ‘serial 7s’ – this, or **dyscalculia** (dysarithmetria), a lesser form, may be acquired or developmental). People with nominal dysphasia are aware of the deficit. A temporary inability to remember a proper noun or name, a universal experience, is called **lethologica**.

A lesion of the angular gyrus leads to loss of ability to read and write (speech, both in terms of production and understanding, is normal), the two kinds of visually mediated language. **Alexia**³²¹⁰ is loss of ability to grasp the meaning of written or printed words or sentences. *Dyslexia* includes word blindness and a tendency to reverse read or written letters and words.

There may be associated neurological deficits in dysphasic patients, e.g. right hemiplegia (Broca’s aphasia), hemianaesthesia and hemianopsia (Wernicke’s), or all of these (global).

Attention

The ability to focus in a sustained way on the matter in hand.

Concentration is the ability to hold that focus.

Latent inhibition refers to the situation wherein a person becomes used to ignoring a stimulus because of its irrelevance, but when its once again becomes relevant the subject finds it difficult to learn its significance³²¹¹.

Terminology around the subject of attention varies somewhat. Krabbendam and Jolles (2002) define attention as a multifactorial construct that includes the capacity to remain alert, orient to new stimuli, to filter what is relevant, and to rapidly discriminate stimuli; sustained attention allows one to be ready to respond to small environmental changes; and sustained attention allows one to focus on the relevant, ignoring the irrelevant. Sustained attention (vigilance) is often measured with the *Continuous Performance Test*³²¹² (CPT). The *Stroop Colour-Word Test* (reading words, naming colours, and an interference condition of names printed in conflicting colours, e.g. ‘BLUE’ written in red) is often used to assess selective attention.

The related concept of **alertness** has been divided into *phasic* (a warning stimulus raises the level of attention), *divided* (ability to attend to more than one stimulus simultaneously and to react to whatever is relevant), and *sustained or vigilant* (maintaining attention on a task over a long period of time). Whilst focal brain damage may selectively impair one of these subtypes, mixed patterns of different degrees of severity are common.

Consciousness

A state of mind which refers to the nature of a person’s mental experience at a given moment in time; to be conscious is to be aware of oneself and ones environment; consciousness may be clouded, that is incomplete or diminished; preoccupation may narrow consciousness so that elements foreign to the preoccupation are excluded from consideration; the lay use of consciousness refers to an awareness, e.g. ‘I was conscious of your dilemma’. From a biological viewpoint, consciousness is a product of tegmental nuclei of the brainstem reticular activating system; diffuse projections go to the forebrain and diencephalon.

Torpor: A state of abnormal drowsiness – patient is sleepy, everything is slowed down³²¹³, perception is diminished in range, concentration requires great effort, and, unlike in functional stupor, amnesia often occurs following resolution of torpor.

Dysarthria

Speech disorder caused by mechanical problems with anatomical structures necessary for articulation of speech. Cerebellar speech involves fluctuations in rate, volume and tone, giving the false impression of intoxication.

Dyspraxia (apraxia)

Absence of praxis.

Motor dyspraxia (lesion of dominant premotor frontal cortex or anterior corpus callosum, or diffuse cortical disease) – ask patient to mime simple tasks such as brushing teeth or copy unusual hand postures demonstrated by examiner.

Constructional dyspraxia (especially lesions of non-dominant hemisphere) – inability to construct shapes, by drawing or other means, either on request or when asked to copy a particular design such as a three-dimensional cube, a clock face, or a bicycle; ask patient to light a match (a complex task) to test for ideomotor/ideational dyspraxia (Q.V.).

Buccofacial apraxia: patient unable to execute the normal facial, lip, and tongue movements, and the problem is not simply due to paresis; severe cases may be almost mute (*aphaemia*).

Ideomotor dyspraxia: the patient cannot mime an action (e.g. hair combing, using scissors, or lighting a cigarette) but can carry out the action when given the actual implements (like a comb)

In **ideational dyspraxia**, on the other hand, there is defective carrying out of both actions (miming and real).

In **dressing dyspraxia**, the patient has difficulty putting on clothing (e.g. puts on garments backwards or puts arm in wrong sleeve).

³²¹⁰ The lesser form is called *dyslexia*.

³²¹¹ This phenomenon is lacking to a significant extent in people with schizophrenia. The latter may be less influenced by prior experience, a phenomenon that might have some relevance for the genesis of hallucinations.

³²¹² Letters or digits are presented singly in random order and subject must respond when a designated target stimulus appears, although there are variations in practice.

³²¹³ Incl. thinking.

Foreign accent syndrome

A rare disorder in people with lesions of the left frontal cortex: speech is otherwise normal but begins to speak with an accent associated with a country to which he or she has no connection. (see, e.g., Seliger et al., 1992)

Euphoria

Unjustified non-infectious happiness, contentment and unconcern; associated with frontal lobe damage or other organic states.

Ecstasy: rare; extreme well being usually kept private, without overactivity; may feel in communion with God; found in epilepsy, mania, and schizophrenia.

Elation: increased mood that is infectious to others, as in many cases of mania: 'infectious jollity'.

Hypergraphia

Uncontrolled excess writing that is correct from a linguistic viewpoint but is nevertheless semantically loose. Causes include CVA, epilepsy, brain tumours, and CJD.

Logoclonia

Spastic repetition of terminal syllable: 'I'm going to the circus, cus, cus, cus.' Found in Parkinson's disease.

Memory

There are 3 functions of memory that are routinely tested by psychiatrists: immediate (primary), recent (secondary), and remote (tertiary).

Testing Memory						
Function	Accessibility	Capacity	Duration	Site of damage	Function	Test
Immediate	Rapid	Limited	Up to 1 minute	RAS*	Register new information	Repeat string of numbers
Recent	Slower	Larger	Mins/years	Limbic	Retention/recall	Repeat 3 objects**
Remote	Slow	Immense	Permanent	AC***	Crucial+	E.g. wars, childhood, jobs

*RAS, reticular activating system. **After 3-5 minutes of distraction. ***Association cortex. +Personal significance of information influences ability to remember.

Palilalia

Repetitions of one's own words, as distinct from *echolalia*, the repetition of the words of other people and *coprolalia*, the uttering of obscenities. However, palilalia is often used to mean repetition of the last uttered word or phrase uttered by others. (Sanchez-Ramos, 2004, p. 296)

Perseveration

Same answer is repeatedly given to different questions, or same non-verbal response is given for different stimuli; common in dementia and frontal lobe syndrome; includes palilalia and logoclonia. A patient may never get dressed because he keeps opening buttons each time he closes them!

Pleiotropy

A single cause can lead to a wide range of behaviours; a gene can manifest different phenotypes, as in Marfan's syndrome.

Reduplicative paramnesia

A (variously defined) delusional belief that one is somewhere other than where one objectively is or, whilst incorrectly describing their true locality, patients hold that a familiar place has many copies in different localities; the actual place where the person is may be novel to that person; described by Pick in 1903; often associated with neurological deficit, e.g. head injury or stroke, especially involving both frontal lobes.

Subtypes of reduplicative paramnesia:

- Place reduplication** – 2 identical places exist to which the patient gives the same name, but the places are situated at a distance from one another
- Chimeric assimilation** – 2 places become one, as when a patient believes that home and hospital are one
- Extravagant spatial localisation** – belief that one is in another place, often one that one knows well

Wada test

Inject sodium amytal directly into each carotid artery: when dominant hemisphere is perfused the patient becomes briefly aphasic.

Witzelsucht

Silly, loud humour, pranks and punning; indicates organic cause, e.g. frontal lobe disease; *morla* is childish excitement or silliness in frontal lobe disease.

Lesions

Hirano bodies: small, eosinophilic rod- or carrot-shaped bodies; may be found in/close to hippocampal pyramidal neurones; contain microfilament protein actin; numerous in AD.

Lewy bodies: laminated intracytoplasmic inclusion bodies in melanin-containing neurones of substantia nigra; derived from neuronal cytoskeleton; are often seen in surviving substantia nigra cells in Parkinson's disease; also found in pigmented cells of locus coeruleus, dorsal vagal nucleus and reticular formation; with development of concept of Lewy body dementia, it became clear that these eosinophilic intraneuronal inclusion bodies have a core of phosphorylated and non-phosphorylated neurofilament protein, microtubule protein, the protein ubiquitin and tau protein and can be found in cerebral cortex³²¹⁴. Antibodies to ubiquitin and alpha-synuclein can be used in postmortem tissue as a method of detecting Lewy bodies. The first genetic cause of Parkinson's disease was reported in 1997: a mis-sense mutation altering fifty-third amino acid of the alpha-synuclein protein (A53T). Shortly thereafter, alpha-synuclein was found in Lewy bodies. Discovery of another mutation (A30P) followed. Genetic triplication³²¹⁵ is associated with onset of Parkinson's disease and dementia with Lewy bodies in the mid-thirties. Genetic duplication³²¹⁶ also leads to disease in some European families. Triplication is far more likely to be associated with dementia than is duplication.

Neurofibrillary tangles (NT) appear as coils of argentophilic tangled bundles. On electronmicroscopy, they are made up of paired helical filaments. The tangle is formed from tau protein itself derived from microtubules. Tau protein in AD is abnormally phosphorylated by protein kinases, less soluble than normal, and unable to bind to microtubules. Glycogen synthase kinase-3 (GSK-3) is an important enzyme in this phosphorylation process. Such abnormal phosphorylation of tau causes neurofilaments to become cross linked and hence form insoluble complexes. Heavily phosphorylated tau does not bind to microtubules, leading the latter to collapse. Many affected neurones die and disappear in the latter stages of Alzheimer's disease, leaving *ghost tangles*³²¹⁷. NTs are usually confined to the hippocampi in normal ageing, whereas in dementia they are more widespread and prevalent. NTs are found in almost every person surviving to the tenth decade.

Pick bodies: rounded, perinuclear condensations of straight (contrasting with helical Alzheimer) filaments found in cortical neurones; contain cytoskeletal elements that bind polyclonal antibodies against neurotubules and a monoclonal antibody against neurofilaments.

Pick cells: cortical neurones that have been expanded and enlarged (ballooned) by argyrophilic bundles of neurofilaments.

Senile plaques (SP): group of abnormal argyrophilic neuritic processes together with reactive microglia and astrocytes arranged in roughly spherical formation, with (mature SP) or without (immature SP) extracellular amyloid core; this amyloid is amyloid beta-protein, derived from a precursor, amyloid precursor protein; gene for amyloid precursor protein (APP) is on chromosome 21.³²¹⁸ Amyloid beta-protein is a normal physiological product. It is hypothesised that amyloid beta-protein deposition leads to tau phosphorylation, tangle formation and cell death (amyloid cascade). Also been suggested that amyloid precursor protein gene mutations alone can account for all pathology found in AD. SP occur in 75% of people who reach their ninetieth birthday.

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³²¹⁴ Temporal, hippocampal, cingulate, limbic and neocortical areas.

³²¹⁵ 3 copies of α -synuclein gene on one chromosome 4 and one copy on the other chromosome 4 = 4 genes.

³²¹⁶ One extra copy of the α -synuclein gene = 3 genes.

³²¹⁷ Tangles without a neurone: especially common in hippocampus.

³²¹⁸ q21; By way of contrast the genes for presenilins 1 and 2 are on chromosomes 14 [q24] and 1 [q31-42] respectively; like amyloid precursor protein, these are associated with early onset Alzheimer's disease. Presenilins are gamma-secretases (aspartyl proteases) that cleave APP into the 42 amino acid version of amyloid peptide (A β 1-42).

22

Old Age Psychiatry

Chapter edited by Henry O'Connell

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I am delighted to welcome publication of the Old Age Psychiatry section, edited by Dr Henry O'Connell. It is very much a practical and clinically oriented document, written by Clinicians for Clinicians. It covers the core clinical areas covered by all jobbing Old Age Psychiatrists in urban and rural settings, and serves as a useful framework for Medical students, Psychiatrists in Training as well as all members of our Multidisciplinary Teams. I particularly welcome the development of this textbook geared for an Irish setting. The section on Delirium by Professor Dave Meagher is particularly relevant in view of the large Liaison Psychiatry component to our clinical work. In addition, with the expected silver tsunami and expansion in our older population, the concomitant increase in cases with Dementia will be particularly challenging for all of us working in the field. A clear overview of this topic is extremely helpful. The sections covering "functional" illnesses depression and psychoses includes a welcome section on Anxiety disorders and a very relevant chapter on Alcohol Use Disorders. The inclusion of chapters on Psychotherapies, Pharmacotherapy and Capacity highlights the breadth of Clinical work for this important specialty. I hope all will find this a practical aide memoire both in the clinic and in the community.

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The complexities and co-morbidities associated with dementia and other mental health problems in older people means that the Old Age Psychiatrist is unique among clinicians in having a vital role in all clinical contexts, including acute psychiatric inpatient care, extended and long-term psychiatric care, nursing-home care, Consultation-Liaison Psychiatry on acute Medical and Surgical wards and in the provision of Day Hospital and home-based assessment and treatment. Older people with mental health problems often present with atypical features requiring specialist assessment and diagnosis and treatment is further complicated by comorbid medical illness and frailty, complex social problems and emerging cognitive impairment and dementia. Dementia itself is a devastating and ultimately terminal condition with wide-ranging cognitive, psychological, social and physical impacts on the individual sufferer, their family and carers and wider society. The practice of Old Age Psychiatry is, therefore, complex and challenging, requiring wide-ranging clinical skills and experience. Furthermore, the Old Age Psychiatrist must constantly advocate for individual older people and for the development of services for older people both locally and nationally. The ageing of populations worldwide means that the absolute number of older people with mental health problems and dementia is expected to rise exponentially in the coming years. All of these factors combine to make Old Age Psychiatry not only a core psychiatric speciality but one of most important of all medical specialities.

Old Age Psychiatry began as a speciality in the United Kingdom and subsequently in Ireland in the late 1980s, in an effort to address the complex needs of older people with dementia and other mental health problems. Older people were, and continue to be, liable to a 'double-whammy' of problems, associated with stigmatised attitudes towards people with mental health problems that is further complicated by problems related to ageism. Even within mental health services, the specific needs of older people are frequently ignored.

There are now approximately thirty public Old Age Psychiatry services in Ireland, covering most geographical regions and at various stages of development, with some private services. However, there is still only limited or no Old Age Psychiatry service available in significant tracts of the country.

This chapter is written by clinicians and for clinicians. The chapter reflects the clinical practice of Old Age Psychiatry, with the first half relating to dementia and delirium and the second half relating to 'functional' mental disorders.

I would like to take this opportunity to thank most sincerely all of the contributors for giving of their time and effort to make this chapter possible.

Dementia

Walter Enudi

Diagnosis and clinical evaluation

Dementia is divided into cortical and subcortical types, based on the site of the primary pathology. The clinical features of cortical and subcortical dementia are shown below in Table 1;

Table 1

Cortical dementia	Subcortical dementia
Early deterioration of memory (amnesia)	Slowing of thought
Early deterioration of language (aphasia)	Relative sparing of memory and language
Early deterioration of visuospatial ability (apraxia)	Difficulty with complex tasks

Early deterioration of face and object recognition (agnosia)	Apathy
	Impaired coordination

The patterns of cognitive deficits in dementia have helped in correlating brain structure and function. The relative preservation of episodic learning often discriminates between Alzheimer's disease and other dementias like Vascular Dementia, with patients having better verbal recall and better contextual verbal delayed recall in Dementia with Lewy body (DLB) and better multimodal retention in Frontotemporal Dementia (FTD).

Diagnosis

A detailed history is an important part of the assessment and emphasis should be placed on the mode of onset, course of progression, pattern of cognitive impairment and presence of non-cognitive symptoms such as behavioural disturbance, hallucinations and delusions. A good collateral history from a relative or carer is also essential as dementia patients may not be able to give a reliable history. The diagnostic criteria for probable Alzheimer's disease using the DSM-IV or ICD-10 have good diagnostic accuracy with a sensitivity of up to 80%. The National Institute of Neurologic, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association group (NINCDS-ADRDA) criteria for probable Alzheimer's disease is also widely used. However, there are few studies looking at the diagnostic accuracy of criteria for Vascular Dementia compared to Alzheimer's disease. This is further complicated by the fact that patients often present with mixed pathology of Vascular Dementia and Alzheimer's disease, and available diagnostic criteria are inadequate in identifying patients with this mixed picture.

The diagnostic criteria in ICD-10 Alzheimer's disease are summarised below

- Presence of dementia
- Insidious onset usually with slow deterioration
- No clinical evidence of systemic or other brain disease which can induce dementia
- Absence of sudden onset or focal neurological signs

DSM IV criteria for dementia of the Alzheimer's type

- Impaired ability to learn new information or to recall previously learned information
- One or more of the following: aphasia, apraxia, agnosia, disturbance in executive functioning
- Significant impairment in social and occupational functioning
- Gradual onset and continuing cognitive decline
- Absence of systemic, neurological or substance induced conditions

The clinical features of Vascular Dementia are variable depending on the underlying pathology and the common presenting features are

- Abrupt onset or step wise deterioration
- Fluctuating course
- Preservation of insight and judgement
- History of stroke
- Focal neurological symptoms or signs
- Depression or emotional lability

The diagnostic criteria for Vascular Dementia using ICD-10 and DSM-IV are summarised below:

ICD-10 criteria for vascular dementia

- Uneven impairment of cognitive function
- Clinical evidence of focal brain damage, manifest as at least one of the following:
 - (1) Unilateral spastic weakness of the limbs
 - (2) Unilaterally increased tendon reflexes
 - (3) Extended plantar response
 - (4) Pseudobulbar palsy

Evidence of significant cerebrovascular disease which may reasonably be judged to be aetiologically related to the dementia

DSM-IV criteria for vascular dementia

- Memory impairment
- One or more of the following cognitive disturbances
 - (a) Aphasia (language disturbance)
 - (b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) Agnosia (failure to recognise or identify objects despite intact sensory function)
 - (d) Disturbance in executive function
- Symptoms cause significant impairment in social or occupational functioning
- Evidence that cerebrovascular disease has caused these deficits

Dementia with Lewy Bodies

There are no ICD-10 or DSM-IV diagnostic criteria for Dementia with Lewy bodies (DLB) but there is a consensus criteria proposed by McKeith *et al* (2006) for the diagnosis of DLB which are summarised below:

Core features

Two of the following core features are essential for a diagnosis of probable DLB and one is essential for possible DLB. Deficits on tests of attention and/or of frontal sub-cortical skills and visuospatial ability may be especially prominent.

- Progressive cognitive decline of sufficient magnitude with interference of normal social or occupational function
- Fluctuating cognition
- Visual hallucinations
- Spontaneous motor features of Parkinsonism

Supportive features

- Repeated falls/syncope
- Transient loss of consciousness
- Autonomic dysfunction
- Systematised delusions

Suggestive features

- REM sleep behaviour disorder
- Severe neuroleptic sensitivity
- Low dopamine transporter uptake in basal ganglia on Positron Emission Tomography (PET) or Single Photon Emission Computerised Tomography (SPECT)

Frontotemporal Dementia

As with DLB there is a consensus guideline, the Lund-Manchester guidelines (Lund and Manchester group, 1994), for the clinical diagnosis of Frontotemporal Dementia and these are also summarised below;

Core features

- Insidious onset and gradual progression
- Early decline in social interpersonal conduct
- Early emotional blunting
- Early impairment in regulation of personal conduct

- Early loss of insight

Supportive features

Behavioural disorder

- Decline in personal hygiene and grooming
- Mental rigidity and inflexibility
- Hyperorality
- Perseverative and stereotyped behaviour
- Utilisation behaviour

Speech and language

- Altered speech output
- Echolalia
- Perseveration
- Late mutism
- Stereotypy of speech

Physical signs

- Incontinence
- Primitive reflexes
- Rigidity, akinesia and tremor
- Low and labile blood pressure

Investigations

- Significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia or perceptuospatial disorder.
- Brain imaging: predominant frontal and/or anterior temporal abnormality.

Clinical examination in Dementia

Full physical including neurological examination is essential in the evaluation of patients with dementia. Conducting a physical examination is essential in also ruling out reversible medical causes of cognitive deficits such as hypothyroidism. The presence of gait abnormalities might be suggestive of normal pressure hydrocephalus.

A detailed mental state examination is paramount in the overall assessment of patients with dementia. Appearance and behaviour give an idea of the severity of the dementia and raises safety concerns. The presence of speech problems such as hesitancy and word-finding difficulties are common. Disturbances in mood are common in dementia and one must also

assess for suicidal thoughts and ideas of harm to others. The presence of visual hallucinations early in the condition and parkinsonism may suggest DLB.

Cognitive Assessment

There are various tools used in the cognitive assessment and the extent to which clinicians assess cognitive function varies widely. The *Mini-Mental State Examination* (MMSE) developed by Folstein et al (1975) as a screening instrument for dementia is widely used. The limitation of the MMSE is its inability to detect very mild dementia, especially with subcortical features. The MMSE results in superficial assessment of memory, language and visuospatial function. Executive functions are not tested and in such cases the Montreal Cognitive Assessment (MOCA, Nasreddine et al, 2005) is more appropriate.

The *Addenbrooke's Cognitive Examination* (ACE) is a more comprehensive measure of cognitive function that incorporates the MMSE. The MMSE should be used in the diagnosis of dementia in individuals with suspected cognitive impairment and the assessment can be improved by the use of *Addenbrooke's Cognitive Examination* or the MOCA. The *Informant Questionnaire on Cognitive Decline in the Elderly* (IQCODE) is a short questionnaire completed by someone who knows the patient and can be a useful adjunct to direct cognitive testing.

Functional Assessment

Diagnosis of dementia invariably affects the individual's daily living skills and ability to perform activities of daily living (ADL) such as feeding, toileting and grooming. Instrumental ADLs (IADLs) include complex activities such as meal preparation, banking and driving. These changes in functional abilities correlate with cognitive deficits and also impact on carer burden that in turn impacts on the risk of institutionalisation. Tools such as the *Bristol Activities of Daily Living* tools are used to assess level of functional impairment. Patients could also be referred to Occupational Therapy for more detailed functional assessment where tools such as the *Assessment of Motor and Processing Skills* (AMPS) are commonly used.

Investigations

Reversible causes of cognitive impairment such as hypothyroidism and vitamin B₁₂ deficiency are rare but must be screened for in each individual assessment. Routine dementia screen involves:

- ✓ Full Blood Count
- ✓ Urea and electrolytes
- ✓ Liver function tests
- ✓ Thyroid function tests
- ✓ Vitamin B₁₂
- ✓ Folate
- ✓ Fasting glucose
- ✓ ESR
- ✓ CRP
- ✓ Urine microscopy, culture and sensitivity
- ✓ CT/MRI brain

Neuroimaging

Brain imaging can be used to detect reversible causes of cognitive impairment and to aid in the differential diagnosis of dementia. Structural imaging should form part of the diagnostic workup of patients with suspected dementia. The choice of imaging technique varies widely and includes Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). SPECT may be used in combination with CT to aid the differential diagnosis of dementia if the diagnosis is in doubt.

CT/MRI Neuroimaging findings in dementia:

Alzheimer's disease	Generalised cerebral atrophy, ventricular enlargement, widened sulci (MRI/CT) Hippocampal atrophy (MRI)
Vascular dementia	Variable depending on pathologies. Single infarct or multiple cortical lesions. Periventricular and deep subcortical lesions and/or lacunae in basal ganglia in subcortical ischaemic vascular disease
Dementia with Lewy bodies	Generalised cerebral atrophy. Relative sparing of medial temporal lobes (MRI)
Frontotemporal Dementia	Focal frontal/temporal atrophy that can be asymmetrical. Knife edge atrophy (MRI)

Management

Treatment of dementia requires a multi-disciplinary approach addressing four core areas; treating the disease, treating the symptoms, supporting the patient and the caregiver. The currently available anti-dementia drugs are not disease modifying but the management of dementia presently is aimed primarily at managing the cognitive and neuropsychiatric symptoms associated with dementia. The treatment involves pharmacological and non-pharmacological treatment, and using both treatment modalities has been found to have better outcomes than either alone.

Pharmacological Intervention

It is important to consider certain factors when starting medication in the elderly. It is well known that older people are more prone to adverse effects of drugs and this is due to the pharmacokinetic changes (e.g. decreased renal clearance and slowed hepatic metabolism) along with higher levels of comorbid medical illness and higher levels of polypharmacy. Therefore, it is advisable to consider these factors when starting medication in the elderly and to start at low doses and go slowly as tolerated.

Acetylcholinesterase Inhibitors:

In Alzheimer's disease (AD), abnormalities in cholinergic neurones are among the prominent neuropathological changes, leading to a cholinergic deficit. Therefore, inhibiting the enzymatic breakdown of acetylcholine should reduce the impact of these abnormalities. A meta-analysis comparing the tolerability and effect on cognition of the three acetylcholinesterase inhibitors, Donepezil, Galantamine and Rivastigmine in people with dementia indicated that there is no difference in efficacy among the three drugs but that Donepezil is better tolerated at therapeutic doses.

Donepezil: Evidence supports the use of Donepezil in people with mild to moderate Alzheimer's disease. There are some benefits for the use of Donepezil in people with Vascular Dementia of mild to moderate severity as revealed by a systematic review. It has also been shown that Donepezil is effective in reducing psychotic symptoms and a limited number of behavioural problems in people with mild to moderate dementia.

Galantamine: Galantamine is effective for the maintenance of cognition in people with mild to moderate Alzheimer's disease. There is also evidence of some benefits in people with mixed Alzheimer's and Vascular Dementia. Higher doses of Galantamine are more effective than lower doses but no added benefit is seen at doses above 24mg daily.

Rivastigmine: Rivastigmine has been shown to have benefits on cognition and global function in people with mild to moderately severe Alzheimer's disease. It is also effective in treating people with Dementia with Lewy Bodies and effective in reducing anxiety and hallucinations.

The doses and common side effects of acetylcholinesterase inhibitors are shown in the table below;

Drug	Dosing	Common side effects
Donepezil	Start 5mg daily then increase to 10mg in 4 weeks	Nausea, headache, diarrhoea
Rivastigmine	Start 1.5 mg twice daily, increase by 1.5mg bd every 2 weeks to maximum dose of 6 mg twice daily. Also available as topical preparation: 4.6mg once daily for 4 weeks increased to 9.5mg once daily thereafter.	Nausea, vomiting, diarrhoea, dizziness Nausea, vomiting, diarrhoea
Galantamine	Start 4mg bd (or 8mg XL daily), increase by 4mg bd every 4 weeks to maximum of 12mg bd (or 24mg XL daily)	

Memantine

Memantine is licensed for the treatment of moderately severe to severe Alzheimer's disease. It acts as an antagonist at N-Methyl-D-Aspartate (NMDA) receptors, which may be neuroprotective and disease modifying. The starting dose is 5mg daily and this should be increased by 5mg weekly to maximum dose of 20 mg daily. Common side effects are headache, dizziness and somnolence.

Non-pharmacological intervention

A wide range of non-pharmacological interventions should be considered in the management of dementia. Behavioural therapy using Antecedent-Behaviour- Consequence (ABC) assessment has been shown to improve behaviour which is sustained. Other therapies that have been used are music therapy, multi-sensory stimulation, reality orientation and validation therapy. There is little evidence that they work and they are often difficult to implement in real-world settings, which may lead to an over reliance on medications.

Caregiver intervention programmes, ranging from simple reassurance to comprehensive caregiver support packages have been shown to delay institutionalisation.

Behavioural and Psychological Symptoms of Dementia (BPSD)

This is a term used to describe a wide range of psychological reactions, psychiatric symptoms and behaviours seen in people with dementia.

Behavioural disturbances

Agitation
 Aggression
 Sleep disturbance
 Inappropriate sexual behaviour
 Hyperorality
 Wandering
 Repetitive behaviours

Psychological symptoms

Depression
 Anxiety
 Misidentification
 Reduplications
 Paranoia
 Delusions
 Hallucinations

These symptoms are usually more distressing to those who care for people with dementia compared to the cognitive features and are often the reason for referral to psychiatric services. Evidence has shown that paranoia and aggressive behaviour is predictive of institutionalisation. In assessing people with BPSD, pharmacological treatment is usually not the first option. It is important to establish the nature and frequency of the symptoms as well as behavioural analysis looking at the antecedents, the context in which the behaviours occur and the consequences. Before considering any intervention, assess for risk to self and others and establish why the behaviour is a problem. In the absence of the above factors, intervention may not be necessary. Some of the non-pharmacological interventions have already been mentioned above, though for some, therapies are limited.

Pharmacological management of BPSD Clusters

BPSD can be conceptualised to comprise of three main clusters of symptoms: psychomotor agitation; aggression and psychosis. Although there is limited evidence supporting the use of medication in the management of BPSD, it is still usually considered as the last option especially if risk to self or others is an issue, and to reduce the level of distress to people with dementia.

- **Psychomotor agitation, including pacing, walking aimlessly, restlessness, repetitive actions, sleep disturbance.**

Trazadone has been found to be useful especially if agitation is associated with depressive symptoms. It also increases slow wave sleep (SWS) and therefore might benefit those with sleep disturbance.

Low dose Lorazepam (0.5mg) is also found to be useful but only in the short term because of the risk of tolerance, dependence and falls. Lorazepam may also cause paradoxical reactions in the elderly.

- **Aggression including verbal and physical aggression especially with high likelihood of risk to self and others and failed non-pharmacological treatment.**

Choice of medication is an atypical antipsychotic, either Olanzapine or Risperidone, but both are associated with increased risk of stroke. Note that all antipsychotics are associated with increased risk of stroke in people with dementia especially in those with vascular risk factors. Avoid using neuroleptics in dementia with Lewy bodies: if necessary, then Quetiapine may be the best choice.

- **Psychosis: hallucinations, delusions and misidentification**

Atypical antipsychotics are the treatment of choice and the above concerns regarding treatment with antipsychotics should be taken into consideration. The lowest possible dose should be used and the need for continued use should be checked regularly, especially after a sustained period of stability.

Course and prognosis

The median survival from diagnosis for AD is about 6 years, which is similar for Vascular Dementia. Neuropsychiatric features and behavioural disturbance become more frequent as the disease progresses.

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DEMENTIA

Chidinma Anamah

Introduction

In dementia there is a decline of higher mental function and previously held abilities. Memory, judgement, thinking, planning and general processing of information are affected.

It is usually regarded as an acquired disorder of the elderly but in 1 in 1000 people symptoms start before age 65. This deterioration according to the WHO should be present for at least 6 months. It should also be severe enough to affect functioning. This is as opposed to Mild Cognitive Impairment (MCI) in which the individual has a measurable deficit in cognition in the absence of dementia and the cognitive deficits do not affect functioning.

Epidemiology

According to the Alzheimer's Society 1 in 1000 people younger than 65yrs has a dementia but by age 80 the rate increases to 1 in 5.

The table below shows the projected prevalence of dementia in Ireland.

YEAR	PERSONS WITH DEMENTIA
2006	37,746
2011	42,441
2016	49,153
2021	58,044
2026	70,115
2031	85,847
2036	103,998

Classification

Dementia can be classified based on age at onset and pathology and aetiology.

Age at onset

Dementia occurring before age 65 is termed Presenile or Early Onset Dementia with aetiological causes of which are more varied and in some cases potentially reversible. Late onset dementia occurs after age 65 and causes are mainly degenerative.

Pathological changes

- Cortical- Alzheimer's disease, Frontotemporal dementia and Creutzfeldt-Jacob disease
- Subcortical- Parkinson's disease, Huntington's disease, Normal pressure hydrocephalus, Multiple Sclerosis
- Mixed-Dementia with Lewy Bodies, Vascular dementia, Corticobasal Degeneration and Neurosyphilis

Aetiology

Degeneration	<ul style="list-style-type: none"> • Alzheimer's disease • Frontotemporal Lobar degeneration • Dementia with Lewy bodies • Parkinson's disorder related dementia • Huntington's disorder
Vascular	<ul style="list-style-type: none"> • Single or multi-infarcts • Cerebral haemorrhage • Binswanger's disease • Vasculitides with CNS involvement • Cardiac disorders
Infections	<ul style="list-style-type: none"> • Syphilis • HIV • TB • CJD
Nutritional deficiencies	<ul style="list-style-type: none"> • Vitamin B12 • Folate
Metabolic, endocrine & inflammatory	<ul style="list-style-type: none"> • Cushing's syndrome • Hypo/hyperthyroidism • SLE • Sustained uraemia • Parathyroidism • Multiple Sclerosis • Sarcoidosis
Toxins	<ul style="list-style-type: none"> • Carbon monoxide • Lead • Arsenic
Others	<ul style="list-style-type: none"> • Normal Pressure Hydrocephalus • Trauma- severe or repeated head injury e.g. in boxers. • Alcohol

Causes of dementia include:

1. Degeneration

The vast majority of dementia is caused by degenerative changes to the brain. These include Alzheimer's Dementia (AD), Frontotemporal Lobar Degeneration, Dementia with Lewy bodies (DLB), Parkinson's disorder related dementia and Huntington's disorder.

Alzheimer's dementia is the commonest cause of dementia at older age, less prevalent before age 65, but still the most common cause of Early Onset Dementia. There is general decrease in the brain weight with atrophic changes. These changes are as a result of abnormal deposits of amyloid proteins and tau proteins in the form of neurofibrillary tangles which release neurotoxic substances that are neurotoxic. The amyloid deposits in AD are composed of beta amyloid proteins. Most cases occur sporadically but rare cases of early onset dementia are inherited as an autosomal dominant disorder that causes mutations in the Amyloid Precursor Protein, Presenilin 1 and Presenilin 2 genes. These genes are located on chromosomes 21, 14 and 1 respectively.

In DLB there is the presence of Lewy bodies which are abnormal proteinaceous cytoplasmic inclusions throughout the brain. In addition to deterioration in memory and other cognitive functions, DLB is also associated with frequent falls, motor features of parkinsonism and well-formed detailed visual hallucinations. Degenerative changes localised to mainly the frontal and temporal lobes cause Frontotemporal Lobar degeneration. This can occur with or without the presence of Picks bodies (Pick's disease). This disorder is associated with early changes in personality and behavioural difficulties. It occurs more commonly in early onset dementia than with the elderly. Huntington's chorea is a rare disorder that has autosomal dominant inheritance with complete penetrance. There is atrophy of the caudate and onset of symptoms could be as early as in adolescence. It is associated with choreiform movements and schizophrenia like features in addition to cognitive decline. Other degenerative causes include corticobasal degeneration and progressive supranuclear palsy.

2. Vascular

These could arise from a single or multi-infarcts, cerebral haemorrhage, vasculitides with CNS involvement, cardiac disorders and Binswanger's disease. Cognitive deterioration in vascular dementia occurs in a step-wise manner i.e. symptoms remain the same for a period of time with intermittent rapid periods of decline.

3. Trauma

Subdural haemorrhages and other traumata to the brain increase the potential for developing dementia.

4. Infections

Infections associated with the development of dementia include syphilis, HIV and TB. A less common infectious cause of dementia is Creutzfeldt Jacob disease, a prion disorder. There are spongiform changes to the brain tissue. Amyloid deposits here are made up from infectious prion protein.

5. Nutritional deficiencies

Decrease in folate and vitamin B12 can cause dementia.

6. Metabolic, endocrine and inflammatory conditions

Metabolic, endocrine and inflammatory causes of dementia are potentially reversible.

7. Toxins

Carbon monoxide, chronic exposure to lead, arsenic and other such toxins are potential causes of dementia.

8. Alcohol

Prolonged heavy use of alcohol and periods of alcohol withdrawal increase glutaminergic neurotransmission in the CNS which is neurotoxic.

9. Other causes

Include normal pressure hydrocephalus (potentially reversible).

Clinical features

People with dementia may present with any combination of behavioural, emotional and psychiatric difficulties as a result of their cognitive decline. This in turn will affect their functioning and ability to carry out activities of daily living.

Onset of difficulties for degenerative causes of dementia could be insidious and family members may report minor changes over months. An acute or subacute onset would suggest a metabolic disorder, toxins or hydrocephalus. A stepwise deterioration is suggestive of vascular type cause.

History

Symptoms may include

1. Deterioration in memory with family members reporting person being more forgetful, losing things, forgetting conversations and asking questions over and over again.
2. There may be complaints of reduced attention, concentration and generally becoming more distractible.
3. Difficulty carrying out and completing tasks. This could be from complex tasks to patients requiring assistance with day to day tasks like cooking, dressing, meals shopping etc. Decline in memory, judgement and general slowing of thought processing can pose potential risks to the patient e.g. leaving a gas cooker on, operating machinery, driving, handling finances.
4. Neuropsychiatric symptoms: depression, anxiety, emotional lability, paranoia, hallucinations and delusions. These symptoms occur intermittently and can lead to agitation and aggressive behaviours. Whilst hallucinations are less common than delusions, visual hallucinations occur early in Dementia with Lewy Bodies.
5. Behavioural symptoms: family may report intermittent periods of agitation and aggression. This could result from the patient's paranoia, anxiety, depression or confusion. Frustration arising from word finding and speech difficulties can also lead to agitation. Wandering behaviour can also arise from increased restlessness. Disinhibition and inappropriate sexualised behaviours occurs in a small percentage of people with dementia. Behaviours reported include making sexualised comments even to strangers, openly masturbating and inappropriately touching people. Compulsive behaviours and rituals have also been reported e.g. turning on and off light switches, constantly going to the bathroom, gathering and collecting certain items, setting fires, cutting things etc. These behaviours can sometimes reflect previous occupations, hobbies and premorbid personality.
6. Personality changes: persons have been described by family as not being their usual selves e.g. becoming more irritable, suspicious, constantly needing reassurance.
7. Speech/language difficulties-word finding difficulties, difficulty naming objects, receptive and expressive language difficulties.
8. Difficulty recognising familiar places and faces.
9. Confusing dates and time
10. Symptoms associated with possible aetiology e.g. family history, medical history of hypertension, strokes, Parkinson's disease, coronary artery disease history of excessive alcohol use, head injury etc.

Physical Examination

Clinical features on physical examination are usually non-specific but could also point to the aetiological cause of the dementia. Tremors, bradykinesia and rigidity could be seen in DLB and features of raised blood pressure and hemiparesis from a previous cerebrovascular accident could indicate a vascular dementia.

Neurological examination may show ataxia, nystagmus and ophthalmoplegia with excessive alcohol related cognitive impairment, such as the Wernicke-Korsakoff syndrome. Gait abnormalities and urinary incontinence could be seen in Normal Pressure Hydrocephalus. As causes of dementia could be mixed, the findings on physical examination could also be varied.

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Delirium

David Meagher

Introduction

Delirium is an acute complex neuropsychiatric syndrome that is characterised by generalised disturbance of brain function occurring in the context of physical illness. The term has subsumed a range of synonyms that (e.g. acute confusional state, brain failure, toxic encephalopathy, intensive care psychosis) that reflect delirium occurring in particular patient groups or treatment settings.

It is estimated that around 10-15% of general hospital patients have delirium upon admission with a further 10-40% developing delirium during hospitalisation. Overall frequency is estimated at 11-42% (Siddiqi ea, 2006), with the clinical rule of thumb that one in five general hospital in-patients experience delirium at some time during hospitalisation. Delirium is especially common in the elderly, those with pre-existing cognitive problems and those receiving intensive care or in hospice and nursing homes.

Symptoms and differential diagnosis

During the 20th century, delirium was described as a 'clouding of consciousness' but this rather nebulous concept has been replaced by the recognition that delirium involves a disproportionate disturbance of attentional processes, diminished grasp of the surrounding environment, and

impaired higher order thinking reflected in disorganised or illogical thought processes and impaired abstraction and comprehension.

Delirium involves generalised disturbance of cognitive functioning and include problems with orientation, visuospatial function, short and long-term memory but attention is disproportionately affected and considered the cardinal cognitive disturbance of delirium. Inattention includes distractibility, reduced vigilance or concentration, and impaired environmental awareness. This contrasts with dementia where memory deficits are cardinal.

Thought process abnormalities in delirium include loosened associations, circumstantiality and tangentiality and result in disorganised thinking. This can be elicited through general observation during the interview and/or proverb interpretation. Disruptions of sleep-wake cycle are a core element of delirium and often predate the appearance of a full-blown episode. These involve sleep fragmentation or even complete sleep-wake cycle reversal and thus are more severe than the insomnia that is a common problem in hospitalised patients. Similarly, alterations in patterns of motor activity are also very common and are used to define clinical subtypes (hypoactive, hyperactive, mixed) (Meagher, 2009). Hypoactive cases are especially prone to non-detection or misdiagnosis as depression. Agitated depression or severe mania can mimic hyperactive delirium but the affective lability of delirium contrast with more sustained alterations in mood and affect in major mood disorders. Psychotic symptoms occur in approximately 50% of delirious patients. Delusions are typically poorly-formed and usually relate to persecutory themes of impending danger or threat in the immediate environment (e.g. being poisoned by nurses) rather than the more complex stereotyped delusions of functional psychosis and dementia. Hallucinations commonly involve the visual modality whereas auditory modalities tend to dominate in mood and functional psychotic disorders.

Delirium onset may be abrupt as with concussion, drug intoxication or stroke, or can be preceded by a prodromal period characterised by anxiety, sleep disturbance, cognitive impairments and increased levels of perceived distress (Gupta et al, 2008).

Diagnosis and detection

ICD-10 and DSM-IV share key features used to diagnose delirium (i.e. acute onset, fluctuating course, inattention, and disorganised thinking). DSM IV is more inclusive and preferred in research studies. Delirium is poorly detected in clinical practice with more than 50% of cases missed, misdiagnosed, or diagnosed late. This reflects the complex and fluctuating nature of delirium symptoms, inadequate education and interview skills of non-psychiatrists, under-appreciation of the prognostic significance of delirium, and inadequate routine cognitive screening in real world practice. Delirium does not have a pathognomonic feature but the range of symptoms (cognition, thought, language, sleep-wake cycle, perception, affect, and motor behaviour) and their pattern over time (acute onset with fluctuating course) are highly characteristic. Delirium diagnosis is also complicated by comorbidity, where over 50% of cases are superimposed on dementia or other pre-existing cognitive impairments. Distinguishing delirium from the neuropsychiatric symptoms of dementia can be challenging but acute onset, fluctuating course, temporal relationship to an identifiable physical precipitant, prominent inattention and altered level of consciousness usually allow differentiation. Third party informants and previous medical charts can clarify baseline cognitive functioning. Studies comparing symptoms of delirium and dementia indicate that where they co-exist, delirium symptoms dominate the clinical picture.

More consistent detection of delirium can be achieved with regular monitoring for any acute deterioration from baseline function coupled with regular formal assessment with simple cognitive tests such as the digit span, reciting the months of year backwards, serial sevens test or clock drawing (Meagher & Leonard, 2008). The *Confusion Assessment Method* (CAM) (Inouye et al, 1990) is a screening tool to assess for four key diagnostic features of delirium. Psychiatrists and delirium specialists use more detailed instruments (e.g. the *Delirium Rating Scale-Revised-98* (DRS-R98) (Trzepacz et al, 2001) and the *Memorial Delirium Rating Scale* (MDAS) (Breitbart et al, 1997) that have specific cut-off scores to identify delirium. In clinically challenging situations,

generalised slowing of the dominant posterior rhythm on the EEG can be used to help differentiate delirium from other neuropsychiatric disorders.

Delirium can be the first indicator of serious physical morbidity (e.g. stroke) and represents a medical emergency. It is not surprising therefore that non-detection is associated with poorer outcomes that include elevated mortality (Kakuma *et al*, 2003). Given the poor prognostic implications of delirium, a possible diagnosis of delirium assumes diagnostic precedence over other neuropsychiatric disorders and the clinical rule of thumb is that suspicious presentations should be considered to be delirium until proven otherwise.

Risk Factors

Delirium is a multifactorial condition where the cumulative effects of predisposing risk factors, individual patient vulnerabilities, and precipitating aetiological insults result in an episode of delirium. A wide range of patient, illness, and treatment variables increase the likelihood of developing delirium but pre-existing cognitive impairment, age extremes, and exposure to particular medications are particularly robust predictors of delirium across populations. The interaction between predisposition (baseline vulnerability) and precipitating insults account for delirium incidence. Inouye and Charpentier (1996) developed a model of 4 common predisposing and 5 precipitating factors that predicted a 17-fold variation in delirium risk in elderly medical patients. Baseline vulnerability is especially important such that minor insults can precipitate delirium in those with multiple predisposing factors.

Aetiology

Single-aetiology delirium is the exception with typically 3-4 significant causative factors relevant over the course of any single episode. It is thus important to remain vigilant to the possibility of multiple aetiological factors and to constantly re-evaluate throughout a delirium episode.

Neuropathogenesis

Delirium reflects generalised disturbance of brain function as evidenced by the broad range of neuropsychiatric symptoms, diffuse slowing on EEG, and widespread alterations in cerebral blood flow. Despite the many possible aetiological factors that contribute to delirium, the clinical presentation is remarkably consistent suggesting that delirium is a unitary syndrome reflecting a final common neural pathway for multiple diverse causes and pathophysiologies (Trzepacz *et al*, 2007).

The prevailing neurochemical theory for delirium posits a relative imbalance of dopaminergic and cholinergic systems and is supported by evidence from preclinical studies, causation of delirium by agents that impact upon these neurochemical systems, and evidence for the effectiveness of dopamine blockers in delirium treatment. Other neurochemical systems (e.g. serotonergic, glutamatergic, GABAergic, noradrenergic) are also implicated in delirium due to particular aetiologies, perhaps through their interactions with dopaminergic and cholinergic systems. Current research is increasingly focusing upon inflammatory mechanisms, disruptions to the stress axis and disturbed oxidative metabolism as possible mechanisms in delirium pathogenesis (Trzepacz *et al*, 2007).

Course and outcomes

The course of delirium is highly variable reflecting the heterogeneity of aetiology and patient populations in which delirium occurs, with many recent studies emphasizing that it is frequently not the benign and transient condition that was previously thought. While in many cases delirium is brief (hours to days), represents a transitional state from unconsciousness or is a benign reaction to treatment exposures, in other cases it can be more prolonged or associated with serious complications and persistent cognitive difficulties where differentiation from dementia becomes difficult (MacLulich *et al*, 2009).

Delirium episodes are associated with elevated morbidity, longer hospital stays, greater costs of care, and higher frequency of complications (NICE, 2010). Moreover, in the elderly, reduced post

hospital independence and elevated 1-year mortality rates occur. A recent study found that the risk of mortality increased by 11% for each additional 48 hours of active delirium (González *et al.*, 2009). Other work has highlighted how experiencing an episode of delirium can accelerate the course of a pre-existing dementia (Fong *et al.*, 2009). Importantly, these adverse outcomes are independent of factors such as age and severity of physical morbidity and are predicted by the presence and severity of delirium itself.

Management

The multifactorial nature of delirium means that optimal management requires the collaborative efforts of primary treating physicians and nursing staff with delirium specialists. Treatment is focused upon addressing the underlying aetiological causes as well as controlling delirium symptoms. Family and loved ones can assist in detection of changes in behaviour and mental state ('not themselves') and provide information about baseline cognitive and adaptive functioning and risk factor exposure.

Delirium can be prevented by multi-component interventions that address modifiable risk factors in elderly medical and post-operative populations (NICE, 2010). Common elements include elimination of unnecessary medications, careful attention to hydration and nutritional status, pain relief, correction of sensory deficits, sleep enhancement, early mobilisation, and cognitive stimulation. Careful attention to reorientation strategies (e.g. clearly visible clock/calendar), safety in immediate surroundings and optimal level of environmental stimulation (e.g. natural levels of diurnal lighting) are fundamental to the management of delirium across treatment settings and populations (Meagher, 2001).

Recent studies of pharmacological prophylaxis of delirium indicate that use of small doses of haloperidol (Kalisvaart *et al.*, 2005), olanzapine (Larsen *et al.*, 2007), risperidone (Prakanrattana & Prapaitrakool, 2007) and melatonin (Al-Aama *et al.*, 2010) can reduce the incidence of delirium in high risk populations.

The pharmacological management of delirium has been poorly studied and although there are over 20 prospective studies of antipsychotic agents, well designed placebo-controlled studies remain lacking. Existing evidence suggests that more than two-thirds of treated delirious patients experience clinical improvement, typically within a week (Meagher & Leonard, 2008). There is little evidence to suggest differences in effectiveness for typical vs atypical agents (Hua *et al.*, 2006), although the few randomised placebo-controlled trials have focused on the use of quetiapine (Tahir *et al.*, 2010; Devlin *et al.*, 2010). Treatment response includes improved cognitive and non-cognitive symptoms of delirium and does not appear to be closely linked to antipsychotic effect or sedative action.

Benzodiazepines are first line treatment for delirium related to sedative and alcohol-withdrawal or seizures but can aggravate mental state (Breitbart *et al.*, 1996) and increase delirium risk in ICU (Pandharipande *et al.*, 2006) and cancer patients (Gaudreau *et al.*, 2005). Judicious use is thus required. The few studies of pro-cholinergic agents do not suggest significant benefits either in prophylaxis or treatment of incident delirium (NICE, 2010) but further work is warranted.

Both pharmacological and non-pharmacological strategies appear less effective in patients with concomitant dementia perhaps reflecting the inherently poor outcome of elderly demented populations with high physical comorbidity. There are concerns regarding the small but increased risk of cerebrovascular events in demented patients chronically receiving neuroleptics, but the relative risks of short-term use in delirium must be proportionalised against potential benefits.

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Differential diagnosis of delirium vs. other common neuropsychiatric conditions

Factors associated with an increased risk for delirium

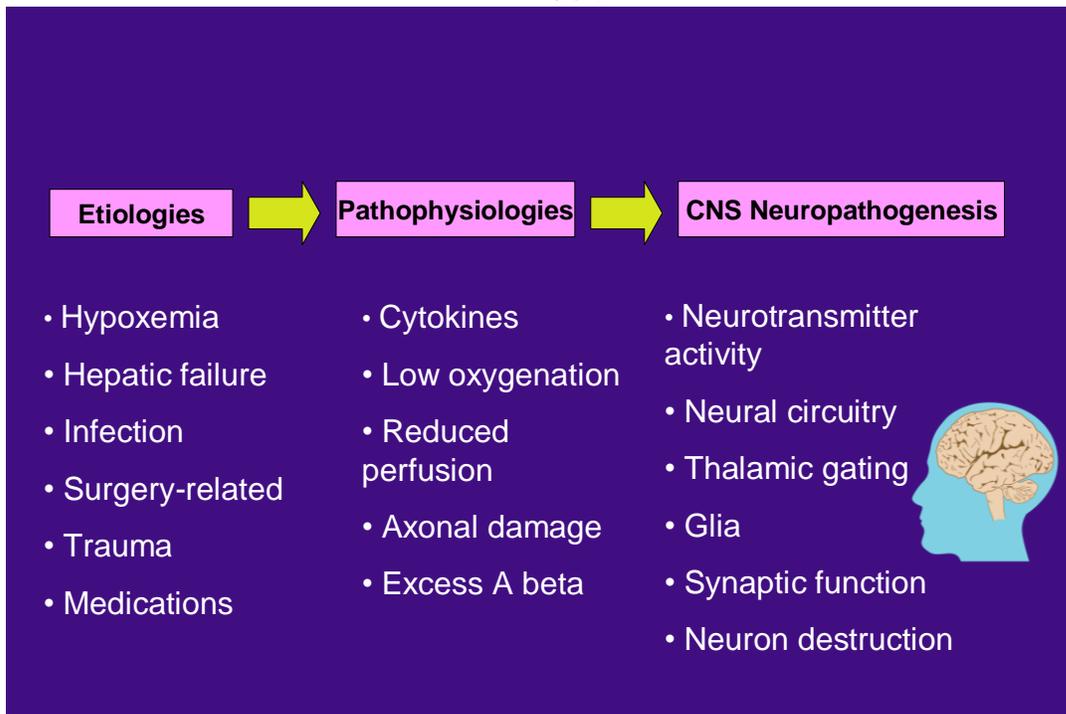
	Delirium	Dementia	Depression	Schizophrenia
Onset	Acute	Insidious*	Variable	Variable
Course	Fluctuating	Often progressive	Diurnal variation	Variable
Reversibility	Frequently	Not usually	Usually but can be recurrent	Chronic relapsing and remitting course typical
Level of consciousness	Impaired	Unimpaired until late stages	Generally unimpaired	Unimpaired (perplexity in acute stage)
Attention/memory	Inattention is primary with poor memory	Poor memory without marked inattention except in end-stage illness	Mild attention problems, inconsistent pattern – depressive pseudodementia, memory intact with formal testing	Poor attention, inconsistent pattern, memory intact
Affect	Lability	No clear pattern	Flattening	Incongruity
Hallucinations	Usually visual; can be auditory, tactile, gustatory, olfactory	Can be visual or auditory	Usually auditory	Usually auditory
Delusions	Fleeting, fragmented, and usually persecutory often relate to immediate environment or impending danger	Paranoid, often fixed, relate to misconceptions	Complex and mood congruent e.g. themes of guilt or nihilism	Frequent, complex, systematized, and often paranoid

*Except for Vascular and Lewy Body Dementia which can be acute/subacute.

1. Patient vulnerabilities
Age extremes
Pre-existing cognitive impairment e.g. dementia, CNS disorder
Genetic factors e.g. APOE genotype
Visual deficit
Hearing deficits
Poor nutritional status
Previous episode of delirium
2. Environmental
Social isolation
Sensory extremes
Immobility
Novel environment
Stress
Use of restraints
ICU stay
3. Medical

Severe medical illness Burns HIV / AIDS Organ insufficiency Infection (eg,UTI) Hypoxemia Fracture Hypothermia / fever Metabolic disturbances Dehydration Elevated BUN Low serum albumin Nicotine withdrawal Increased blood-brain barrier permeability Uncontrolled pain
4. Procedure-related Peri-operative Type of surgery (e.g. hip) Emergency procedure Duration of operation Urinary Catheterization Artificial respiration
5. Drug-related Polypharmacy Drug / alcohol dependence Psychoactive drug use Specific agents (e.g. anticholinergics / opiates/ benzodiazepines)

Examples of different aetiologies for delirium and a variety of pathophysiological mechanisms that can then alter brain function. The neuropathogenesis of delirium involves dysfunction of brain regions and circuitry which may ultimately result in characteristic symptoms of delirium despite a wide variety of aetiologies and pathophysiological insults to the brain.



MOOD DISORDERS

Oliaku Eneh

Depression

Definition

Depression is a mood disorder that is characterized by persistent sadness that has gone beyond the normal every day fluctuations in mood and adversely affects one's view of self, the world and the future and can infringe on the individual's level of functioning, depending on the severity. It is often recurrent but the first episode is likely to be associated with a stressful life event.

Depression is common in the elderly. However, it is not recognized frequently nor treated adequately in this age group and the clinical picture may vary to a greater or lesser extent from that seen in younger adults and is often complicated by co-morbid dementia and physical illness. In addition, the loneliness associated with loss of a spouse and other social difficulties contribute in making elderly people more vulnerable to depression.

Epidemiology

According to the DSM-IV criteria for major depression, community prevalence is up to 9.4%, higher in hospitals (approximately 12%) and nursing homes (approximately 42%) and doubles after the age of 70 with a male: female ratio of approximately 1:2 (Rodda ea, 2008).

Aetiology

In most cases it is difficult to isolate a single cause as many factors come into play to determine a person's susceptibility for depression. Therefore, the term risk factors are used to describe some situations that could predispose a person to develop depression in later life. The most important risk factors for depression in later life are (Rodda et al, 2008):

1. Genetic predisposition: though it remains somewhat significant, the genetic risk of developing depression in later life is thought to be less than that of adolescents or younger adults.

2. Physical illness: This accounts for a large proportion of depression in the elderly. The risk of depression increases with severity of medical problems. Although there are certain diseases that are known to be associated with an increased risk, any debilitating illness can lead to the development of depression in older persons. The disease conditions with the greatest risk of depression include:

- Cardiovascular disease, mainly myocardial infarction (25% have minor depression and 25% have major depression) and hypertension.
- Cerebrovascular disease: mainly ischaemic stroke (Vascular Depression)
- Carcinoma (25-38% of cancer patients suffer from depression)
- Endocrine disorder, mainly thyroid and parathyroid disorders, adrenocortical insufficiency or hyperactivity, Cushing's disease and Diabetes mellitus (the prevalence of depression in diabetic patients is 20%).
- Parkinson's disease (50% of patients with Parkinson's disease have depressive symptoms)
- Malnutrition.
- Nutritional deficiency e.g Vitamin B12.
- Dementia.
- Infection

3. Neurotransmitter theory: there is evidence to show that depression is closely linked to depletion of neurotransmitters such as serotonin and noradrenaline.

4. Social isolation, deprivation and stressful life event: Loneliness and lack of companionship especially that of a confiding one possibly due to bereavement is significantly associated with late onset depression. Low socioeconomic status, role transition like retirement and increased dependency due to frailty and poor physical health are also contributory factors.

5. Vulnerable Personality: anxious and dependent personality disorders increase the vulnerability of certain elderly people to depression and are also poor prognostic indicators.

6. Drug induced: steroids, hormones, antihypertensives (clonidine, methyldopa, beta-blockers, calcium channel blockers, ACE inhibitors, reserpine), statins, H2 receptor antagonists like cimetidine, drugs used in oncology like tamoxifen, vinblastine and vincristine, analgesics like NSAIDs, antiparkinsonian drugs, some antibiotics, alcohol and illicit substances.

Clinical Features and Diagnosis

According to the ICD-10 diagnostic criteria (WHO, 1992), key clinical features include:

- Low mood which may be worse in the mornings*
- Loss of interest and enjoyment, also called anhedonia.*
- Reduced energy levels leading to increased fatigability and diminished activity.

The above are the 3 major symptoms that are usually present.

Other associated symptoms which may be present depending on the severity include:

- altered sleep pattern leading to early morning waking (>2 hours before normal)*
- reduced appetite sometimes leading to weight loss of up to 5% or more body weight in past month*
- diminished concentration and attention
- low self-esteem and self confidence
- feelings of guilt and worthlessness
- negative view of the future which may sometimes border on hopelessness
- anxiety and irritability
- loss of libido*
- motor agitation or retardation*
- decreased emotional reactivity*
- thoughts of self harm, passive death wish or active suicidal ideation.

Co-occurrence of up to 4 of the symptoms marked with asterisk constitutes a somatic syndrome. These symptoms should be present for at least two weeks to warrant a diagnosis for all degrees of severity but a shorter duration may suffice if the symptoms are exceptionally severe. This description is valid for all age groups including the elderly.

Depressive episodes can be sub-divided into 3 varieties: mild, moderate and severe, each of which presents with varying degrees of the symptoms mentioned above.

A **mild depressive episode** consists of 2 or more major symptoms plus at least 2 other symptoms with or without somatic syndrome. There is usually preservation of normal function.

A **moderate depressive episode** consists of 2 or more major symptoms plus at least 3 or 4 other symptoms with or without somatic syndrome. There is considerable reduction in normal function.

A **severe depressive episode** consists of all 3 major symptoms plus at least 4 other symptoms including prominent feelings of guilt, futility and low self esteem in addition to passive death wish or active suicidal ideation with or without psychotic features.

If the depressive episode recurs, then the term **recurrent** is used to describe it. If the depressed mood becomes chronic lasting for several years but is too mild in severity and too short in duration to fulfil the criteria for any of the categories listed above then the term **dysthymia** is used.

In the elderly, somatic complaints, reversible cognitive impairment (the so-called 'pseudo-dementia'), anxiety, psychomotor agitation and psychotic symptoms (delusions of guilt, nihilism, persecution, hypochondriasis) may be the prominent symptoms.

It is important to recognize pseudo-dementia, which presents with definite onset and short duration of memory impairment. Low mood precedes the onset of subjective memory impairment, insight into memory difficulties is well preserved, patient's may be unwilling to answer questions on cognitive testing, often saying, with frequent 'I don't know' or 'I can't' type answers.

Neuropathological changes

In late life, as a result of vascular disease there are ischaemic and inflammatory changes in key brain areas especially the dorsolateral, prefrontal cortex leading to increase in glia and astrocyte activity in addition to MRI signal hyperintensities in the deep white matter in contrast to younger adults where there seems to be glial reduction³.

Abnormalities of frontostriatal circuitry, amygdala and hippocampus, which may be related to both aging and hypercortisolaemia are also noted (Rodda et al, 2008).

Management

After a thorough history, mental state and cognitive function examination, any underlying physical illness should be detected and treated with review of current medications. The general model for treatment follows the same principle as in younger adults and includes the following types of intervention:

- Pharmacological/biological** (antidepressants)
- Psychological** (cognitive behavioural therapy, interpersonal therapy and problem-solving therapy)
- Social** (welfare benefits, housing issues, joining groups for social interaction and support, etc.)

The psychological and social interventions require input from other allied healthcare professionals (Psychologist, Social Worker and Occupational Therapist) and lend a holistic approach to the treatment.

In mild depression and dysthymia, 'watchful waiting' is appropriate unless symptoms persist for longer than two to three months, when treatment should be started using the model above.

In moderate and severe depression, immediate treatment is indicated also using the above model, inpatient admission may be required especially if thoughts of suicide are prominent and switching to or combining with a different class of antidepressant, augmentation using lithium or electroconvulsive therapy (ECT) may become necessary if there is inadequate response. If psychotic features are part of the presenting symptoms of depression, an atypical antipsychotic or ECT may be used in addition.

The choice of antidepressants is clearly at the discretion of the treating psychiatrist but NICE guidelines recommend selective serotonin reuptake inhibitors (SSRIs) as first line because of their safer side effect profile, they are safer in over-dose and can cause nausea and other gastrointestinal symptoms but are relatively free of cardiotoxicity, postural hypotension and anticholinergic side effects seen with Tricyclic antidepressants. Venlafaxine and Mirtazapine are second line drugs while the Tricyclic antidepressants and Moclobemide (Mono-amine Oxidase Inhibitor) are third line and side effects must be carefully considered before prescribing. The elderly are likely to be on several medications due to concurrent illnesses so the risk of drug interactions and drug induced problems are high. The general rule is to start at a low dose and increase very gradually if necessary ('start low and go slow').

The duration of treatment should be for at least one year after resolution of symptoms and, if the condition is recurrent, treatment may be further prolonged and in some cases may be lifelong.

Prognosis

In determining the long term outcome of late life depression, the confounding effects of physical illness, cognitive impairment, social stressors, long term mental illness and different management approaches should be borne in mind. There is evidence to suggest that 21% of elderly patients with depression will have died and almost 50% will still have depression.

The highest risk of completed suicide worldwide is among the elderly and up to 83% of elderly suicides have a diagnosis of depression. Therefore, enquiring about thoughts of self harm and suicide is a crucial part of mental state examination in this age group and must not be overlooked. There is evidence to show that depression also increases the non-suicide related mortality in elderly patients.

Bipolar Affective Disorder

Definition

Bipolar affective disorder (BPAD) is a mood disorder that manifests with repeated periods of low mood alternating with periods of elevated mood and, in between these two phases, there are intervening periods of completely normal mood during which the individual maintains optimal function.

Onset of mania after the age is 65 is relatively rare and is often associated with an organic or neurological illness, less likely associated with a positive family history of affective disorder and is classified as secondary mania. In the majority of elderly patients with BPAD, the onset is usually in young adulthood. As with depression, the management of BPAD in the elderly is similar to that of younger adults.

Epidemiology

Data regarding incidence and prevalence of mania in the elderly shows some trends (Shulman, 1993). The incidence, as measured by first admission rates to hospital, increases with age even in the extremes of old age. However, the community prevalence decreases with age. The one year prevalence rate of BPAD decreases with age: prevalence is about 1.4% in those aged 18-44, 0.4% in those aged 45-64 and 0.1% in those aged 65 and over. Only 10% of all cases of BPAD present after the age of 50 and male: female ratio in the elderly is 2:1. Mania represents up to 12% of all affective disorders treated on specialized psychiatric geriatric units and average age of onset is 55 years, often preceded by repeated episodes of depression by up to 16 years.

Aetiology

As with unipolar depression, the aetiological factors for BPAD in the elderly are multiple and include:

1. Genetic predisposition: first degree relatives of patients with BPAD have 25-50% increased chance of developing the illness. Earlier age of onset is associated with a positive family history while co-morbid neurological disorder has lower genetic predisposition
2. Organic or neurological disease (secondary mania) - the likelihood of an organic aetiology increases with age. The prevalence of organic brain disease in mania ranges from 20-40% with significant increase in cognitive impairment and cerebral atrophy noted on CT scan. Cerebrovascular disorders, chronic alcoholism, head injury and right sided brain lesions are the most common brain diseases associated with secondary mania
3. Substance misuse
4. Personality traits (Cyclothymic personality)
5. Social deprivation
6. Adverse life events, especially loss events
7. Neurotransmitter theory (serotonin, noradrenalin and dopamine have been implicated).
8. Drug induced- antidepressants, antiparkinsonian drugs (levodopa, bromocriptine, amantadine), steroids, cardiovascular drugs (captopril, methyldopa, clonidine, propranolol, digoxin, diltiazem), antibiotics (clarithromycin and drugs used in tuberculosis), analgesics (opiates, tramadol, buprenorphine, indomethacin), antiemetics (cyclizine and metoclopramide), H2 receptor antagonists (cimetidine, ranitidine), others (baclofen, chloroquine, interferon, cyclosporine)

Clinical Features and Diagnosis

The cardinal features of mania as stated in the ICD-10 diagnostic guidelines are (WHO, 1992)
 - Elevated mood (elation or euphoria)

- Increase in the quantity and speed of physical (energy) and mental activity (racing thoughts and flight of ideas)
- Other associated symptoms are
- increased sociability
 - talkativeness (pressure of speech)
 - overfamiliarity
 - increased sexual energy with disinhibited behaviour
 - decreased need for sleep
 - poor financial judgement leading to overspending
 - irritability
 - distractibility
 - conceit
 - ill-mannered behaviour
 - impaired concentration and attention
 - inflated sense of self importance (grandiosity) which may lead to the undertaking of unrealistic new ventures and reckless behaviour
 - possession of special talents or powers
 - exaggerated optimism and self esteem

Mania can occur with or without psychotic features depending on the severity and is usually associated with severe or complete disruption of work or other social activities. The most severe form of mania is associated with psychotic features which are mainly mood congruent in the form of grandiose delusions and hallucinatory experiences in the auditory modality specifically in the context of voices talking about the patient's special powers.

The mildest form of mania in which abnormalities of mood and behaviour are too persistent and marked to be classified as cyclothymia is called **hypomania**. In this variety there are no psychotic features, the symptom profile is milder and there is considerable but not severe disruption of work or other social activities with preservation of some degree of functioning.

Cyclothymia is a persistent instability of mood, involving numerous periods of mild depression and mild elation that develops in early adult life and pursues a chronic course. None of the episodes of depression or elation are sufficiently severe or prolonged to fulfil the criteria for BPAD.

In BPAD, the individual suffers from two or more episodes of affective disturbance, either:

- episodes of depression alternating with either mania or hypomania
- or repeated episodes of mania or hypomania

The episodes must last at least one week to warrant a diagnosis.

Rapid cycling bipolar illness is associated with 4 or more affective episodes in a year. It is less responsive to medications and has a poorer prognosis.

Mixed affective state is characterized by a mixture of both manic and depressive symptoms occurring concurrently. Elderly patients present more frequently with mixed affective symptoms. It is treated in the same way as mania.

Neuropathological changes

Neuroimaging studies have confirmed an increase in sub-cortical hyperintensities. Also MRI scans in elderly patients with mania show a high prevalence of deep white matter and sub-cortical ischaemic changes, which may be of aetiological importance.

Management

This follows the same principles as for depression. It is important to investigate thoroughly any elderly patient with first episode mania, looking out for underlying organic or neurological diseases. Neuroimaging techniques like positron emission tomography (PET scan), single photon emission tomography (SPECT) and magnetic resonance imaging (MRI scan) may facilitate the identification of neurological diseases. The interventions include:

-Pharmacological/Biological: evidence is limited regarding the treatment of mania in the elderly.

Lithium retains an important first line role in the acute treatment and prophylaxis of mania and depression in the elderly but beware of increased risk of neurotoxicity. Renal function is compromised in the elderly so 'start low and go slow' applies in relation to initial and subsequent dose administration. Careful blood monitoring is required and target serum level is lower than for younger adults. Treatment is initiated and maintained at approximately half the dose of younger adults.

Anticonvulsants **Sodium Valproate** and **Carbamazepine** are widely used in the acute treatment and prophylaxis of mania and depression due to their mood stabilizing properties. Valproate is an enzyme inhibitor and this may lead to interactions with hepatically metabolised drugs Valproate is not superior to Lithium but it has a better side effect profile and is used as an adjunct in lithium therapy. It is useful in treating rapid cycling illness and secondary mania. A combination of Lithium and Sodium Valproate is more superior than using either drug alone. Carbamazepine is less effective than either Lithium or Valproate and is a liver enzyme inducer, therefore it interferes with the metabolism of other drugs. It has a worse side effect profile than Valproate with potential to cause agranulocytosis, cardiotoxicity and neurotoxicity.

Lamotrigine is effective in treating bipolar depression. Evidence is limited for the use of **Gabapentin** and **Topiramate**.

Antipsychotics like Olanzapine, Risperidone, Quetiapine and Aripiprazole appear to be effective in treating mania but their use in the elderly manic patients is limited by side effects such as extrapyramidal with potential for worsening of parkinsonism, hypotension, sedation, weight gain and diabetes and precipitation of depressive symptoms. Quetiapine seems to have lesser potential for inducing extrapyramidal side effects.

Benzodiazepines are effective in lessening agitation and behavioural disturbances. However, in the elderly their use should be restricted to severe cases because of adverse effects such as sedation, hypotension, falls and paradoxical agitation and confusion.

Antidepressants are effective in alleviating depressive episodes but caution should be exercised because of their potential to induce mania. The protective effect of a mood stabilizer is required before using an antidepressant and as soon as the depressive episode resolves, the antidepressant is usually withdrawn.

After recovery from an acute affective episode in BPAD, prophylactic treatment is continued long-term in elderly patients. The exact duration is not clear but the NICE guidelines recommend a period of two to five years in young adults.

In very severe manic or depressive symptoms, where the patient is either stuporous, has psychotic symptoms, fails to eat or drink, or is not responding to other treatments, **ECT** is valuable.

-Psychological interventions include Cognitive Behavioural Therapy and family interventions. These are helpful as adjuncts to pharmacological treatment.

-Social interventions like resolving housing and financial issues and improving social interactions and vocational involvements are also important.

Prognosis

After accounting for some confounding factors like brain disease, evidence suggests that 34-50% of elderly manic patient will die on long term follow up as against 20% of elderly patients with unipolar depression. Also, 32% will suffer significant cognitive decline, as measured by a score of less than 24 on Mini-Mental State Examination. This suggests that mania has a poorer prognosis and represents a more severe disruption of the central nervous system function.

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Anxiety Disorders

Oliaku Eneh

Definition

The psychological symptoms of anxiety comprise of fear, worry, nervousness, tension, apprehension, irritability, difficulty concentrating and insomnia. The physical symptoms include increased heart rate resulting in palpitations, breathlessness, light headedness and dizziness, nausea, tremor, dry mouth, sweating, abdominal discomfort that may progress to diarrhoea and frequent micturition. Patients may have a tendency to alleviate their symptoms by abusing alcohol and prescribed medications, especially benzodiazepines.

Most psychiatric disorders in the elderly have co-morbid anxiety and many elderly people get very anxious about the multiple health conditions they are faced with, resulting in the under-recognition and under-treatment of primary anxiety disorders.

Classification

According to the ICD-10 diagnostic guidelines, anxiety disorders include the following common disorders

- Phobic disorders
- Panic disorder
- Generalized anxiety disorder
- Mixed anxiety and depressive disorder
- Obsessive-Compulsive disorder
- Post-traumatic stress disorder
- Acute stress reaction
- Adjustment disorders
- Dissociative disorders
- Somatoform disorders

There is considerable co-morbidity within these disorders and between anxiety disorders and depression.

Epidemiology

The prevalence of most anxiety disorders falls with age and is higher in women than in men. This gender difference is less pronounced in the elderly and the majority of cases are longstanding with onset in young adulthood and middle age. However, a significant minority have their onset in old age. Overall prevalence in the elderly ranges from 5-10%, the highest rates are found in the community with phobic disorders presenting the most while panic disorders present the least.

Aetiology

As with other psychiatric disorders, many factors come to play in the development of anxiety disorders in the elderly. They include

1. **Physical illness-** there is an association between anxiety disorders and increased mortality and physical morbidity from cardiovascular, respiratory and gastrointestinal complaints. This is further confounded by the physical symptoms of anxiety with some important physical disorders presenting with anxiety symptoms and vice versa. In the majority of elderly people, the investigations and treatment of physical illness is frightening and may provoke anxiety disorder in vulnerable individuals. The following are some of the physical causes of anxiety in the elderly
 - Cardiovascular (myocardial infarction, cardiac arrhythmias, postural hypotension, mitral valve prolapse, heart failure)
 - Respiratory (pneumonia, pulmonary embolism, COPD)
 - Endocrine (hypo/hyperthyroidism, hypo/hypercalcaemia, hypo/hyperkalaemia, hypoglycaemia, hypothermia, pheochromocytoma, insulinoma, Cushing's disease and carcinoid syndrome).
 - Neurological (dementia, head injury, cerebral tumour, delirium, epilepsy, demyelinating disease)
 - Dietary and medication related (vitamin deficiencies, caffeine, digoxin toxicity, corticosteroids, dopamine agonists, sympathomimetics, akathisia, fluoxetine)

2. **Psychosocial stressors-** evidence shows that anxiety is associated with low socioeconomic status. Adverse life events especially if they are threatening in nature are known to precipitate anxiety. In addition, individuals may also develop late life vulnerability to anxiety when faced with challenges if they were previously exposed to early adverse experience such as parental loss. Anxiety essentially results from inability to utilize effective coping skills. In contrast to late life depression, phobic disorders in the elderly are not associated with the lack of confiding relationships; rather it is believed that in some cases the presence of close relationships may maintain phobic avoidance (Lindesay, 1996) because in a bid to protect and support the patient, families and other home based services invariably encourage the housebound approach and may thereby worsen the situation.

3. **Drug induced-** A variety of drugs have been implicated in the onset of anxiety symptoms. They include:
 - Thyroxine
 - Antidepressants
 - Anticholinergics
 - Sympathomimetics

- Steroids
- Alcohol
- Caffeine

In addition, withdrawal symptoms from psychotropic medications can also precipitate anxiety symptoms (Rodda et al, 2008).

4. Co-morbidity with other psychiatric illness-

- High levels of anxiety are often found in elderly patients in the early stages of dementia.
- Symptoms of anxiety are often associated with depression and when both conditions coexist in elderly people, there is a greater severity of depressive symptoms, an increased likelihood of suicidal ideation, lower social functioning and a negative impact on remission of depressive symptoms (Rodda et al, 2008).

5. **Genetic predisposition-** may contribute to the development of anxiety disorders. Recent studies revealed that different genes showed evidence for association with specific types of anxiety disorders, such as panic disorder, social phobias or generalised anxiety disorder (Academy of Finland, 2008). However this finding is more robust in adult onset anxiety disorders.

Specific anxiety disorders and their clinical features

Phobic disorder

Phobia occurs commonly in the elderly with increasing frailty and prevalence ranges from 0.7 to 13.4% (Rodda et al, 2008). Phobia arises due to irrational fears about specific objects or situations. These disorders provoke clinically significant levels of distress and disability due to high levels of anxiety. They are usually heralded by a traumatic event usually of a physical nature and may have had a public manifestation. However, in spite of the complete resolution of the physical event, the psychological impairment persists.

There are 3 main types of phobia:

Agoraphobia- prevalence in the elderly is estimated to range from 1.4 to 7.9% (Rodda et al, 2008) and according to the ICD-10 criteria, this consists of significant and consistent fear of two or more of the following (WHO, 1992):

- leaving home
- entering shops, crowds and public places
- travelling alone in trains, buses or planes.

These individuals may be rendered housebound because many are terrified by the thought of collapsing and being left helpless in public. It can occur with or without panic attacks but always causes anxiety symptoms during the situation. This fear may spiral out of control if there is no obvious escape route and embarrassment is perceived. Consequently the individual learns to avoid these situations and this avoidance in turn reinforces the fear. Fear can also occur merely in anticipation of the anxiety-provoking situation and symptoms are not better explained by another mental or physical disorder.

Social phobia- onset is usually in adolescence and runs a chronic course. According to the ICD-10 criteria, this consists of:

- significant and consistent fear of scrutiny by other people and being an object of ridicule as a result of negative public evaluation, usually in the context of behaving in an embarrassing and shameful manner. It occurs in the context of small groups rather than crowds.
- experience of general symptoms of anxiety in social situations in addition to either tremors, blushing, fear of vomiting or micturition.
- avoidance of social situations which in turn reinforces this fear and may lead to complete social isolation.

Fear can also occur merely in anticipation of social situations. Symptoms are not better explained by another mental or physical disorder.

Specific phobias- fear is experienced only in the presence of a particular object or situation. Onset is usually in childhood and prevalence in the elderly is estimated to range from 3.1 to 12%. Examples in the elderly include phobia for height, lightning and flying. Anxiety is restricted to the presence of the specific phobic object or situation, all other diagnostic criteria are similar to those of social phobia.

Panic disorder

Panic attacks and panic disorder are rare and symptomatically less severe in the elderly, estimates of prevalence ranges from 0.1-1%. However, the prominent physical symptoms of panic disorder may result in patients being referred instead to cardiologists, neurologists and gastroenterologists. In one study of cardiology patients with chest pain and no coronary disease, one third of those aged 65 and over met the criteria for panic disorder. It is a chronic condition with a relapsing and remitting course.

According to the ICD-10, the diagnostic criteria for panic disorder includes:

- recurrent attacks of extreme anxiety which develop rapidly and resolve spontaneously after a few minutes.
- attacks occur spontaneously in situations with no obvious danger, are not confined to a particular situation with anxiety free periods in between attacks.

Several attacks occur within a period of one month and symptoms are not better explained by another psychiatric or physical disorder.

Panic attacks are often co-morbid with other psychiatric disorders, particularly depression, and it may be severe enough to mask depressive features.

Generalised anxiety disorder (GAD)

GAD is very common and has a community prevalence of 1.9-7.3% in the elderly. It is more common in women than in men. In 50% of patients, onset is in early adulthood.

According to the ICD 10 criteria, there should be at least six months duration of

- prominent and excessive tension, worry and apprehension about normal everyday issues on most days, not limited to any one object, subject or situation and enough to cause distress and impair function.
- at least four associated psychological and physical symptoms of anxiety resulting from autonomic arousal.

In addition the condition should not meet the criteria for other anxiety disorders, psychiatric or physical disorders.

Obsessive Compulsive Disorder (OCD)

OCD is a distinct disorder involving the orbitofrontal cortex, basal ganglia, substantia nigra and ventrolateral pallidum. It is the most persistent and stable of all the specific anxiety disorders.

Onset in old age is rare, the majority starting before the age of 25 and usually running a chronic fluctuating course into old age especially if left untreated.

Obsessional symptoms may appear at any age following head injury or cerebral tumour.

According to the ICD 10 criteria, obsessions are unpleasant, persistent and intrusive ideas, images or desires that dominate a person's thoughts. The individual recognizes them as originating from his own mind but is unable to resist them despite repeated attempts at doing so. Compulsion is the irresistible urge to perform an act repeatedly despite the futility of that action. The underlying motivation is to prevent a perceived adverse event from happening. Insight is usually fully intact and the patients usually regard these symptoms as unreasonable and are distressed by them so much so that their functioning is impaired to a greater or lesser degree. Obsessions and or compulsions should last at least two weeks and not arise as a result of another mental disorder.

OCD is highly co-morbid with other anxiety disorders, depression, schizophrenia Parkinson's disease and dementia.

Common examples of OCD presentations are cleaning, checking, symmetry, contamination, doubting, and violent thoughts that sometimes have a sexual undertone.

Post traumatic stress disorder (PTSD)

In PTSD, anxiety symptoms are preceded by an event that is exceptionally traumatic and disastrous in nature. The experience of the event is sometimes regarded as "near death" for the individual and might actually have involved the death of another person. Symptoms begin within six months of the event and should be present for more than a month, are severe enough to cause distress and impair functioning. According to the ICD 10 criteria, it involves the following:

- repetitive and intrusive recollection or reliving of the event (flashbacks) with associated recurring nightmares.
- avoidance of situations or places that are reminiscent of the trauma
- and one or more of
 1. Inability to remember certain aspects of the event
 2. Heightened emotional arousal in the form of exaggerated startle response, hypervigilance, emotional numbness, insomnia, irritability and poor concentration that were not there prior to the incident.

Older persons who are frail have a greater tendency to feel threatened than their younger counterparts.

Acute stress reaction

This happens when symptoms of anxiety occur in response to extreme physical or psychological trauma. The risk of developing this disorder is increased if physical exhaustion or organic factors are also present as in the elderly. It is usually of brief duration, onset is within a few hours and it lasts only hours or days. Patient is initially 'dazed' with associated reduction in attention and consciousness, inability to comprehend stimuli and disorientation. This is followed by either withdrawal from the situation or agitation and severe distress, depression, anger and despair.

Symptoms of autonomic arousal are often present.

Supportive counselling is the treatment of choice.

Adjustment disorders

These are similar to an acute stress reaction. The preceding event is a life changing one that is associated with significant subjective distress and emotional disturbance. The major difference is that the anxiety that follows lasts longer and emanates from difficulty in adjusting to the prevailing situation. Onset of symptoms is within one month of the event and duration is usually less than six months. Brief (< one month) or prolonged mild depressive reaction might accompany the anxiety symptoms. Symptoms may impair functioning but do not meet the criteria for another psychiatric diagnosis.

Community prevalence is about 5% and in the elderly, an adjustment disorder often follows physical illness or disability, moving into a residential or nursing home and bereavement.

Supportive psychotherapy, social and occupational support are the mainstay of treatment.

Medications may be necessary for symptoms of anxiety and depression.

Management

Summary of NICE guidelines (Taylor ea, 2007) for the treatment of anxiety disorders:

1. Psychological therapy is more effective than pharmacological therapy and should be used as first line where possible.

This include Cognitive Behavioural Therapy (CBT) with anxiety management for most anxiety disorders, graded exposure to feared situation with relaxation (systematic desensitization) for phobic disorders, exposure and response prevention for OCD, eye movement desensitization and reprocessing (EMDR) and trauma focussed psychological treatment for PTSD.

Self-help (based on CBT principles) should also be encouraged.

2. Pharmacological therapy is also effective but should be used as second line for most anxiety disorders. Most evidence supports the use of SSRI antidepressants for all anxiety disorders.

Panic disorders

Benzodiazepines should be avoided.

If SSRIs are contraindicated or ineffective, Imipramine or Clomipramine can be used but be mindful of the anticholinergic and arrhythmogenic side effects in the elderly. It is imperative to recognize and treat any underlying co-morbid conditions.

GAD

Benzodiazepines should not be used beyond 2-4 weeks. More recent evidence suggests the use of Pregabalin for GAD in the elderly.

OCD

Combination of SSRI and intensive CBT is highly advocated. Use Clomipramine if SSRIs fail and if response is suboptimal, add an antipsychotic or combine Citalopram and Clomipramine. High doses of medication are often required and there may be delay in onset of action of up to 12 weeks.

PTSD

In addition to SSRIs, Tricyclic Antidepressants and Mirtazapine are useful.

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Psychosis

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Definition

The psychoses include disorders which distort the individual's perception and interpretation of reality in combination with inappropriate affect and they are referred to as late paraphrenia if onset is in old age. Sensorium remains intact but deficits in cognitive function may manifest over time. The individual loses their sense of uniqueness and individuality with a persistent feeling that their innermost thoughts and ideas are being infiltrated upon and hijacked by others, with their actions and impulses under bizarre external influences and belief in the validity of these experiences may grow to become unwavering.

There may be perceptual disturbances in terms of delusions and hallucinatory experiences most especially in the auditory modality. Hallucinations in other modalities like olfactory and gustatory may also occur. However, visual hallucinations are often indicative of an organic pathology.

Classification

The major disorders in this category include:

- Schizophrenia
- Schizoaffective disorder
- Delusional disorder

Furthermore, according to the International Late-Onset Schizophrenia Group publication in 2000 there are three groups based on age of onset:

- Early Onset Schizophrenia like illness (EOS) depicts onset before the age of 40.
- Late-Onset Schizophrenia like illness (LOS) depicts onset between the age of 40 and 60
- Very Late Onset Schizophrenia like illness (VLOS) depicts onset after the age of 60 and this is rare.

Epidemiology

Data is scarce but one-year prevalence of LOS is 0.6% and of VLOSP is 0.4%. Community prevalence of VLOSP is 0.1-0.5%.

Aetiology

Risk factors for late onset psychosis include:

1. Female gender
2. Abnormal pre-morbid personality (schizoid and paranoid personality traits)
3. Poor pre-morbid social functioning
4. Social isolation
5. Sensory impairment (mainly deafness)

Genetic predisposition and neurodevelopmental factors have lesser impact than in earlier onset psychosis.

Clinical features

Schizophrenia

The symptoms of schizophrenia are divided into positive (symptoms that are typical only to schizophrenia, they include the group listed 1 to 5 below) and negative (symptoms that are

not typically found only in schizophrenia but may be found in other disorders, they are the symptoms listed on number 6 below).

1. Auditory hallucinations- running commentary, 2nd (includes command hallucinations) and 3rd person or other hallucinatory voices coming from some part of the body.
2. Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception.
3. Persistent delusions that are culturally inappropriate and completely impossible.
4. Thought echo, thought insertion or withdrawal, thought broadcasting.
5. Thought disorder- breaks in the train of thought resulting in incoherent or irrelevant speech or neologisms.
6. Negative symptoms such as flat or blunted affect (apathy), poverty of thought and speech (alogia), inability to experience pleasure (anhedonia), lack of desire to form relationships (asociality), lack of motivation (amotivation). They should not be due to depression or neuroleptic medication.
7. Persistent hallucinations in other modality (olfactory and gustatory hallucinations) when accompanied by delusions without clear affective component, persistent overvalued ideas, occurrence every day for months on end.
8. Catatonia (stupor, excitement, waxy flexibility, negativism, mutism and posturing).

According to the ICD-10 diagnostic criteria, at least the following must be present most of the time for one month to warrant a diagnosis

- a minimum of one very clear symptom in the group listed 1 to 4 above OR
- at least two symptoms from the group listed 5 to 8 above.

The diagnosis of schizophrenia should not be made if depressive or manic symptoms are prominent and extensive unless it is clear that psychotic symptoms predate the affective disturbance.

If both psychotic and affective symptoms develop at the same time, then a diagnosis of schizoaffective disorder should be made.

If affective symptoms predate the psychotic symptoms, then a diagnosis of either mania with psychotic symptoms or depression with psychotic symptoms should be made.

Other associated symptoms are depression, agitation, cognitive impairment and soft neurological signs.

With ageing, there are certain changes that occur in early onset schizophrenia. New positive symptoms rarely develop in old age, but old hallucinations and delusions may persist.

Individuals are often well adjusted to their illness by the time they are older.

Onset in old age

- Thought disorder and negative symptoms are relatively rare.
- Delusions are almost always systematized and mainly of a persecutory and referential nature and often in the context of invasion of privacy by unwanted visitors and neighbours through structural barriers like walls, ceilings and floors (partition delusions). Other common delusions are theft, jealousy, and disease infestation.
- Hallucinations may include auditory, visual, tactile and gustatory.

Early onset

- Thought disorder and negative symptoms are common.
- Delusions can be systematised or non-systematised.
- Hallucinations are almost always auditory.

Neuropathological changes

Findings are similar to those of early onset schizophrenia.

On CT brain scan there is

- Increased ventricle-to-brain volume ratio
- Third ventricle enlargement
- Reduced frontal and temporal lobe or superior temporal gyrus volume

Management

Forming a good therapeutic relationship is imperative and can go a long way in improving medication compliance. Members of the Community Mental Health team should bear this in mind. Patients may require inpatient admission if distress is high and medication compliance is an issue.

1. **Pharmacological treatment-** Atypical antipsychotics are first-line, mainly Olanzapine and Risperidone. The required doses are much lower than for younger adults, as low as one tenth of the standard dose because the elderly are at a greater risk of developing extrapyramidal and other adverse effects, and 'starting low and going slow' is strongly advised.
2. **Psychological treatment-** e.g. Cognitive Behavioural Therapy.
3. **Social interventions-** Day centre and day hospital attendance helps to mitigate social isolation. Treating hearing loss and visual impairment can help reduce sensory deprivation, which in itself can be an aetiological factor.

Prognosis

Late onset schizophrenia may have a better prognosis and response to treatment than early onset schizophrenia. Compliance with medication and good social support are among the predictors of good response. Remission rates of up to 48-61% have been reported.

Schizoaffective disorder

If both schizophrenic and affective symptoms develop simultaneously and are evenly balanced, the diagnosis of schizoaffective disorder should be made even if the schizophrenic symptoms by themselves would have justified the diagnosis of schizophrenia.

Management is similar to that of schizophrenia; however the mood symptoms may need to be treated with antidepressants and/or mood stabilizer medication.

Delusional disorder

This disorder is characterized by the development of either a single delusion or a set of related delusions which are usually persistent and sometimes lifelong. The delusions are often persecutory, hypochondriacal, or grandiose but they may be concerned with litigation, jealousy, or express a conviction that the individual's body is misshapen, or that others think he or she smells. According to the ICD-10, the delusions must be present for at least three months with no persistent hallucinations in any modality. The general criteria for schizophrenia are not fulfilled and the delusions are not typically schizophrenic.

The condition should not be due to other medical or psychiatric disorder and depressive symptoms may be present at other times.

Management involves the use of atypical antipsychotics and CBT focused on the delusional belief.

Prognosis

In general, there is complete remission in 33-50%, noted improvement in 10% and persisting delusions in 33-50%. Acute onset is associated with better prognosis and presence of symptoms for more than six months is associated with poorer prognosis. Long-term treatment is necessary in many cases.

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Alcohol Use Disorders (AUDs) and Illicit Drug Use in Older People

Henry O'Connell

Alcohol Use Disorders (AUDs) is a general term used to describe the wide spectrum of health problems associated with alcohol use, ranging from excessive alcohol consumption above recommended levels through to alcohol abuse and alcohol dependence syndrome.

AUDs in older people tend not to receive as much attention as in younger people for a number of reasons. AUDs in older people are often more clinically silent than in younger people with less obvious social disruption for the individual and society generally (O'Connell ea, 2003; Dar, 2006).

As with many other mental disorders in older people, AUDs in older people may present atypically, thus leading to problems with under-detection and misdiagnosis. Furthermore, when detected, AUDs in older people may not be treated aggressively, because of ageist and therapeutically pessimistic assumptions.

Screening and diagnostic criteria for AUDs may be inappropriate for older people, and recommended levels of intake for the general population may be inappropriately high for older people.

There are few systematic studies that have examined the prevalence of alcohol abuse/dependence in people over the age of 65. A recent study (Blazer & Wu, 2011) examining the prevalence of alcohol abuse, dependence and subthreshold dependence among middle-aged and elderly persons in the United States found that about 6.7% (dependence 0.6%, abuse 0.9% and subthreshold dependence 5.2%) of those older than 65 reported alcohol abuse, dependence or dependence symptoms. Among past-year alcohol users, 15.4% (dependence 1.3%, abuse

2.1% and subthreshold dependence 12.0%) of those older than 65 endorsed alcohol abuse or dependence symptoms. 'Tolerance' (48%) and 'time spent using' (37%) were the two symptoms most frequently endorsed by the subthreshold group.

AUDs in older people are associated with multiple associations and risk factors (see Table 1), and clinical effects are wide-ranging, affecting practically all organ systems (Table 2).

Table 1: Risk factors for substance abuse in the elderly (from Atkinson RM, *Psychiatry in the Elderly*, 2001)

<p>Predisposing factors</p> <p>Family history (alcohol)</p> <p>Previous substance abuse</p> <p>Previous pattern of substance consumption (individual and cohort effects)</p> <p>Personality traits (sedative-hypnotics, anxiolytics)</p> <p>Factors that may increase substance exposure and consumption level</p> <p>Gender (men-alcohol, illicit drugs; women-sedative-hypnotics, anxiolytics)</p> <p>Chronic illness associated with pain (opioid analgesics), insomnia (hypnotic drugs), or anxiety (anxiolytic)</p> <p>Long-term prescribing (sedative-hypnotics, anxiolytics)</p> <p>Caregiver overuse of 'as needed, medication (institutionalized elderly)</p> <p>Life stress, loss, social isolation</p> <p>Negative affects (depression, grief, demoralization, anger) (alcohol)</p> <p>Family collusion and drinking partners (alcohol)</p> <p>Discretionary time, money (alcohol)</p> <p>Factors that may increase the effects and abuse potential of substances</p> <p>Age-associated drug sensitivity (pharmacokinetic, pharmacodynamic factors)</p> <p>Chronic medical illnesses</p> <p>Other medications (alcohol-drug, drug-drug interactions)</p>

Table 2: Physical, neuropsychiatric and sociodemographic aspects of AUDs in older people

<p><u>Gastrointestinal:</u> Hepatic problems: elevated liver enzymes; fatty liver; alcoholic hepatitis; cirrhosis; malignancy <i>Gastritis, peptic ulcer disease and bleeding</i> Oesophageal varices Acute and chronic pancreatitis</p> <p><u>Malignancies:</u> mouth, pharynx, larynx, oesophagus, hepatic, colorectal, pancreatic</p> <p><u>Cardiovascular:</u> Ischaemic heart disease <i>Hypertension</i> <i>Alcohol induced arrhythmias</i> Congestive heart failure Alcoholic cardiomyopathy</p> <p><u>Haematological:</u> Macrocytosis (acute effect of alcohol intake and due to Vitamin B12 and Folate deficiency in chronic AUD) Anaemia (due to gastrointestinal problems)</p> <p><u>Musculoskeletal:</u> Falls and fractures Reduced bone density Myopathy</p> <p><u>Metabolic:</u> Hypoglycaemia Hyperuricaemia Elevated lipids Diabetes more difficult to control</p> <p><u>Neuropsychiatric:</u> Cognitive impairment and dementia Frontal lobe impairment Wernicke-Korsakoff syndrome Cerebellar cortical degeneration Central pontine myelinosis Marchiafava-Bignami disease Depression Psychosis Intoxication <i>Withdrawal syndrome (may be more difficult to treat in older people)</i> Suicide</p> <p><u>Other:</u></p>
<p>Alcohol-drug interactions</p>
<p>Aspiration pneumonia Road traffic and other accidents</p>

Sociodemographic:

Male gender
 Divorced, widowed and single status
 Social isolation
 Upper and lower ends of socio-economic spectrum

Prevention and Treatment of AUDs in Older People

Primary prevention measures focus on preventing the development of *de novo* AUDs in the general population and in older people. Measures such as increasing alcohol cost through taxation and restricting accessing through licensing laws have significant impacts on overall consumption and the level of AUDs in a population. Specifically in older people, clinicians should be vigilant for the development of an AUD in the context of any of the risk factors outlined in Table 1.

Treatment modalities for AUDs in older people can be divided into biological/medical, social and psychological. Biological/medical treatments are most important in the acute setting, where detoxification may be required. In view of increased physical frailty and evidence for more severe alcohol withdrawals in older people (Brower et al, 1994), medical admission is advised for detoxification in older people. Fluid and electrolyte imbalances should be corrected and cognitive state should be monitored regularly in view of the risk of developing delirium.

Care should be taken with benzodiazepine-assisted withdrawal in older people, in view of the elevated risk of over-sedation, confusion and falls. Use of an objective measure of alcohol withdrawal such as the Clinical Institute Withdrawal Assessment for Alcohol-Revised Version (CIWA-Ar) is advisable in defining the severity of alcohol withdrawal and monitoring clinical course, although this scale is not elderly-specific and areas such as 'orientation and clouding of sensorium' may be disproportionately affected in older people, especially if cognitive impairment is present (Naranjo & Sellers, 1986 and see Table 3).

Table 3. The Clinical Institute Withdrawal Assessment for Alcohol-Revised Version (CIWA-Ar) (from The South London and Maudsley NHS Trust Prescribing Guidelines, 2005-2006)

(Items 1-9 are scored from 0-7 and item 10 from 0-4. Maximum possible score is 67).

1. Nausea and vomiting
2. Tremor
3. Paroxysmal sweats
4. Anxiety
5. Agitation
6. Tactile disturbances

- | |
|-------------------------------------------|
| 7. Auditory disturbances |
| 8. Visual disturbances |
| 9. Headaches and fullness in head |
| 10. Orientation and clouding of sensorium |

Severity of alcohol withdrawal

Mild:	<10
Moderate:	10-20
Severe:	20+

Parenteral or oral thiamine should be given to prevent development of the Wernicke-Korsakoff syndrome.

There is limited evidence available on the use of abstinence medications such as Disulfiram, Naltrexone and Acamprosate in older people, and they are probably best avoided in view of elevated risk of adverse effects. However, there is some evidence that Naltrexone may be safe and effective in treating AUDs in older people (Oslin *ea*, 1997a and 1997b).

Psychological treatments include specific psychotherapies focussing on AUDs (e.g. motivational interviewing, addiction counselling) and psychotherapies aimed at comorbid psychiatric disorders. There is some evidence that older people may respond better to psychotherapy in same-age settings, i.e. among other older people (Schonfeld & Dupree, 1995; Kofoed *ea*, 1987), presumably because of a shared experience of the elderly-specific aspects of AUDs. Social aspects of treatment include identifying and addressing problems with personal finances, housing levels of social contacts, as problems in these areas may serve to perpetuate the AUD.

Illicit Drug Use in Older People

*Generations of people reaching old age in the coming decades will carry with them higher levels of illicit drug use than current and past generations of older people (Dowling *ea*, 2008; Patterson & Jeste, 1999).*

As with AUDs in older people, lower levels of drug intake are required to cause harm and presentation may be atypical and thus go undetected.

ICD-10 defines specific diagnostic criteria for intoxication, harmful use, dependence and withdrawal state for a wide range of illegal substances, including opioids (heroin), cannabinoids, cocaine, other stimulants including caffeine, hallucinogens, tobacco and volatile solvents. However, there are no elderly-specific diagnostic criteria.

In the recent NSDUH Report from the USA, the past year non-medical use of prescription drugs was more common than marijuana use among those over age 65 years (0.8% versus 0.4%; Office of Applied Studies, 2009); however, the rates of marijuana use for 'baby-boomers' (those over age 50 years) was much higher at 4.2% and we can therefore expect a rise in the incidence and prevalence of illicit drug use in older people by 2020 as this population ages.

The findings of Amdt ea (2011) demonstrating that the proportion of older adults (defined as 55 years or over in the study) attending for substance use treatment is increasing relative to younger adults, with an increasing illicit drug involvement (cocaine and heroin) in older adult admissions is consistent with a cohort effect of 'Baby-boomers'.

There is currently a dearth of information on clinical features and comorbidity of illicit substance use in older people. Such features will also vary widely depending on the drug in question and the mode of administration.

A thorough history of any current or past use of illicit drugs should be recorded, along with mental state and physical examinations and collateral history, if available. Further investigations will be directed by the type of drug or drugs used, the route of administration and the clinical findings.

It is predicted that by 2020, the number of people over the age of 50 needing substance abuse treatment will double (Han ea, 2009). The ageing 'baby-boom' generation in the US has been cited as a potential source of older illegal drug users (Patterson & Jeste, 1999) and so clinical experience in this area and the need for primary prevention strategies and age-specific treatment programmes will be needed.

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Prescribing in the Elderly

Nola Greene

Age-related changes have profound impacts on pharmacokinetic and pharmacodynamic factors, thus impacting on prescribing practices in older people.

Changes:

Central Nervous System

1. Older people have impaired postural reflexes and increased sway with an associated increased risk of falls.
2. Increased frequency of oral dyskinesias and tremors.
3. Neuronal loss especially in the Cerebellum and Substantia Nigra (gait disturbance) and the Locus Ceruleus (sleep disturbance).
4. Visual and Hearing deficits (difficulty in medication management)
5. Cognitive difficulties (medication management)
6. Sleep changes with ageing include reduced continuity of sleep (frequent awakenings), reduced Stage 4 (slow wave) sleep, phase advancement (earlier REM).

Cardiac

1. Increased systolic blood pressure.
2. Reduced early diastolic filling.
3. Increased susceptibility to heart failure if heart rate increased (c.f. drugs with anticholinergic side effects or those that increase heart rate can lead to heart failure).

Respiratory

1. Increased residual volume.
2. Reduced FEV.
3. Reduced Vital capacity.
4. Reduced pulmonary defence mechanisms (e.g. increased susceptibility to pneumonia in depressed patients who stay in bed).
5. Reduced arterial pO₂ (increased susceptibility to delirium).

Endocrine

1. Increased insulin resistance
2. Slight increase in TSH

Sexual/gender-related

1. In men erections are less firm
2. Increased risk of osteoporosis in post-menopausal women (therefore increased risk of fractures with falls)

Specific changes of ageing affecting psychotropic prescribing:

1. Reduction in renal clearance affecting excretion of e.g. Lithium, Gabapentin, Memantine.
2. Reduction in hepatic blood flow and oxidising systems slowing drug metabolism resulting in increased half life of most psychotropic drugs such as benzodiazepines, antidepressants and antipsychotics.
3. Reduced capacity to conserve sodium can result in hyponatremia, especially with SSRIs.
4. Increase in Fat/Muscle ratio resulting in the accumulation of liposoluble drugs.
5. Reduction in albumin levels resulting in increase in the free fraction of protein-bound drugs.

Overall there is increased heterogeneity apparent, i.e. there is more variety in presentation of illness and in response to drug treatment.

The elderly respond differently than others to physical illness and have easily impaired homeostasis, with less pronounced signs of illness. For example, pneumonia can be present without fever.

The importance of taking a thorough medical history and physical examination cannot be over emphasised.

1. Prescription drugs (enquire about multiple sources such as multiple GP's, hospital specialists) especially analgesics, anxiolytics and sedative hypnotics. Take note of medication with particular neurological or psychiatric side-effects such as anticholinergic drugs, Beta blockers, drugs for Parkinson's disease. Check medication list at each encounter and ascertain what is actually being consumed, which may be different to that which is being prescribed. Always include topical eye drops, often containing anticholinergic and Beta blocking agents.
2. Over the Counter drugs including those with codeine and caffeine. Non-Steroidal Anti-Inflammatory drugs. Laxatives.
3. Herbal, homeopathic medication, vitamins, nutraceuticals, home remedies and other substances sourced from alternative practitioners and 'Health Food' shops.
4. Medication taken on advice from family and neighbours.
5. Consumer direct marketed medication (Internet, mail order)
6. Latterly, the introduction of Nurse prescribed medication.
7. Substance abuse history to include alcohol, Illicit substances (remember middle aged drug addicts become older drug addicts), caffeine, codeine and nicotine abuse.

Those over age 65 years are the greatest consumers of prescribed medication. In the US, in a study of a community dwelling population of older people, 29% took ≥ 5 prescribed medications, 42% took ≥ 1 over the counter medication and 49% took ≥ 1 dietary supplements. The average intake was 5 prescription drugs and 3 non-prescription drugs. (Kennerfalk ea, 2002; Everitt, 1986) Byrne ea (2011) found that long-term residents of Irish nursing homes took a median of eleven medications.

Risk for drug interaction increases with the number of drugs ingested, with an interaction rate of 13% with 2 drugs up to a rate of 82% with 7 or more drugs taken.

Co-morbid disease will influence prescribing not only due to the impact of the disease in addition to the normal physiological changes of ageing, but also by forcing consideration of drug interactions with the medication already prescribed or sourced for these conditions by the patient. Possessing ≥ 3 co-morbidities increases the risk of an adverse drug event (ADE) by three to twelve-fold. (Evans ea, 2005)

Inappropriate prescribing is highly prevalent in older patients, (60% in Irish nursing homes: O'Mahony EUGMS 2010), 73% in Irish long stay facilities for the elderly, and may be even higher in patients attending Psychiatry of Later life services (Greene ea, *in press*).

Potentially inappropriate medications (PIMs) are defined as drugs that pose more risk than benefit particularly where safer alternatives exist, and includes drugs prescribed at inappropriate dosages or for inappropriate duration or where there are clinically significant drug-drug or drug-disease interactions (Gallagher & O'Mahony, 2008).

PIMs are associated with increased risk of ADE's, and increased morbidity, mortality and health care utilisation. (Hamilton ea, 2009).

Drug Utilisation Review Tools used when documenting medication can be useful in detecting PIMs. The best known ones are *Beers' criteria* (US), *Medication Appropriateness Index* (MAI: US), IPET (Canada)) and *Screening Tool of Older Persons' Potentially inappropriate Prescriptions* (STOPP) criteria (Ireland, UK and Europe).

Potentially inappropriate medication prescription may initially present to the psychiatrist acutely as Delirium or as Cognitive impairment.

Apparent treatment resistant depression can be due to ongoing alcohol dependence. Caffeine withdrawal causes recurrent headaches and Anxiety. Without a thorough medication and substance use history, prescription of psychotropic drugs can become part of a treatment cascade whereby increasing amounts of inappropriate medication are prescribed to treat the side effects of previously prescribed medication. The elderly are particularly vulnerable to Medication errors at so called 'transitions of Care', such as on admission and discharge from hospital or nursing homes. Many older people residing at home need supervision or administration of medication either due to psychiatric illness or cognitive impairment. Those who are disorientated in day and time will not be able to manage even with the assistance of 'pill-pot' daily packaging of medication. In summary, the elderly psychiatric patient carries prescribing risks associated with the pharmacokinetics of the ageing body. In addition, older patients more often have multiple co-morbidities and associated increased prescribing from multiple prescribers and are at increased risk of PIMs. Heterogeneity of psychotropic pharmacodynamics in this population demands caution both in initiation and monitoring of drug dosages.

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Psychological interventions in Old Age Psychiatry

Marcel Steenkist

'... Near or above the age of fifty the elasticity of the mental processes on which treatment depends is as a rule lacking – old people are no longer educable...' (Freud, 1905).

It is rather ironic those comments of Freud, then already at the age of 49, having this view on older people. Nevertheless this negative view of age has continued into recent times. This therapeutic nihilism has had a profound effect on the development of both psychotherapy theory and services for older people. Psychotherapy theory has tended to focus on childhood development and the developmental stages of infant, child and early-adult life, with later life being neglected as a developmental phase.

Currently 'Late life' or 'The Third Age' is viewed as an important developmental period that can significantly add to a life well lived, if approached as an important period of growth and psychological development. We may experience a time of vitality during which individuals can expect to explore and develop their potentials. Society makes available social services and living options that did not exist a few decades ago. (Zarit & Knight, 1996).

My aim here is to give readers a brief overview of the psychological therapies that may be used when working with older people. Psychological therapies with older people have traditionally held a low position in Old Age Psychiatry and in psychotherapy generally, mainly due to ageism and negative stereotyping about treatability, especially around the impact of cognitive decline on older people

With the current high demand on Old Age Psychiatry services for the assessment and treatment of early dementia, depression and anxiety, developments in services are focusing on biological models of illness and pharmacological treatments, again at the expense of psychological therapies. Psychotherapeutic interventions require specific additional skills of the clinician and are not always on hand. Secondly, the psychotherapeutic process may not yield immediate

responses and is more time consuming and labour intensive. Many of our clients still want a quick fix. Beck (1976) argued that the combination of a biological approach with a psychotherapy approach yields better results than either of those therapies alone.

While there is no systematic research to suggest that psychotherapies must be adapted for older populations, most experts in psychotherapy with older populations believe that, for older adults to benefit from psychotherapy, the interventions must be modified to accommodate age-related changes in learning, information processing, and health status.

In addition, cohort-related beliefs about mental health and psychotherapy should also be considered. Thus, adaptations made to psychotherapy for older populations include time to socialize older adults to the process of psychotherapy, adjusting the pace of the psychotherapy to account for age-related changes in information processing, and allowing flexibility in the delivery of psychotherapy to overcome medical and physical barriers to care.

Some of the psychotherapeutic interventions are listed below:

Cognitive–Behavioural Therapy (CBT) is the form of psychotherapy most often used with older people. CBT is the evidence-based treatment of choice for several psychiatric disorders, and it is agreed that a person's age should not preclude them from psychological therapies (Department of Health, 2002).

At the same time, older adults with mental health problems should have access to the same range of therapies as those under the age of 65 (Department of Health, 2001).

In controlled clinical studies it has been shown to be efficacious in the treatment of depression, anxiety and problematic behaviours in the context of dementia. For reviews of this literature see Teri (1994) and Wilkinson (2002).

Cognitive Analytic Therapy (CAT) represents a modern integration of analytic (object relations theory) and cognitive psychotherapy traditions to provide a brief, structured and collaborative therapeutic journey from past trauma into reconnection with dialogue and meaning. In existence for less than 20 years, the evidence base, although in progress, is yet to be established, but there is interest in applying the model to older people and potential for the development of a therapy that truly speaks to later life through its emphasis on shared meaning in the context of the client's life story and the recognised importance of the 'dialogue', both cathartic and reparative, in the therapeutic relationship (Hepple, 2002).

Psychodynamic therapy: this broad range of therapies, stemming largely from the work of Freud, Klein and Jung, has been discussed widely in relation to later life. For reviews, see Garner (2002) and Arden (2002). Some empirical evidence exists to suggest that psychodynamic work with older people is at least as effective as CBT in dealing with depression (Thompson et al., 1987).

Interpersonal therapy is a practical, focused, brief manual-based therapy that can be applied by a range of professionals after a period of basic training.

Its accessibility has generated considerable interest in its use with older people, and a reasonable evidence base exists to support its efficacy in the treatment of depression in older people, both in the acute phase and in relapse prevention (Reynolds et al., 1999).

The aim of this brief outline was to give some overview on the therapeutic interventions available and to give some consideration on how to apply them successfully to the older patient group.

If we are really serious about implementing a bio-psycho-social or holistic model, psychotherapy sits comfortably within this model, in whatever shape or form.

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Capacity

Colin Fernandez and Miriam Kennedy

Prior to examining and commencing treatment on a patient, a healthcare professional must obtain valid consent. This respects a patient's autonomy to make an informed decision about their care without coercion. In order to make an informed decision, there is a presumption that an individual possesses the mental 'capacity' or 'competence' to make a decision.

In a medical context and for the purpose of this chapter, 'capacity' is referred to and defined as (Leonard P & McLoughlin, 2009):

- The ability to understand the information that is relevant to the decision.
- The ability to retain the information long enough to make a decision.
- The ability to use or weigh up the information to make a decision.
- The ability to communicate the decision. (Includes talking, sign language and simple motor movements such as blinking or hand squeezing to communicate).

In certain mental states such as severe mental illness, dementia, learning disability, brain damage, terminal illnesses or altered consciousness, one's ability to make a decision may be affected. This is referred to as a lack of 'capacity'. A patient lacking in capacity will not be able to give valid consent. Valid consent is both a legal and ethical requirement prior to examination or commencing treatment. Failure to obtain valid consent on the part of a healthcare professional may lead to serious legal consequences such as charges of negligence and assault.

Capacity may be temporarily impaired due to various factors such as altered consciousness, intoxication or heightened emotional distress and may return following resolution of these states. The assessment of capacity therefore should be repeated as required during the course of treatment if there is any doubt of a patient's capacity.

The principle function of capacity is to safeguard a patient's autonomy. In the presence of capacity, a patient retains the overriding right to consent or refuse treatment or care even if this may seem unwise or go against clinical advice. This emphasizes the core issue in balancing a person's right to autonomy in decision-making with a professional and ethical duty to protect them from harm.

A **functional approach** is recommended when assessing capacity (Arscott, 1997). This involves assessing a specific choice at a specific point in time. The person's functional abilities are assessed in relation to the skills required for decision-making. Judgment is then made as to whether or not the person's abilities meet the demands of the decision in question. The functional approach brings the advantages of greater reliability, acknowledgement of the fluctuating nature

of capacity and therefore a requirement for repeat assessment as required and the possibility of improving an individual's relevant functional abilities (Arscott, 1997).

At present there is no legislation pertaining to capacity in Ireland. There is a move towards a change following an expansion on a template set out by the Law Reform Commission Ireland (Law Reform Commission, 2006) in the form of the publication of the *Mental Capacity and Guardianship Bill* in 2008 and the *Scheme of Mental Capacity Bill* 2008. The Bill proposes a substitute decision-making process for those without capacity through the establishment of a Guardianship Board, an Office of the Public Guardian and appointment of Personal Guardians to assist in decision-making (*Mental Capacity and Guardianship Bill, 2008; Scheme of Mental Capacity Bill, 2008*).

Until this new legislation comes into effect in Ireland, the Wardship system (*Lunacy Regulations (Ireland) Act, 1871*) is the only option for substitute decision-making in Ireland. According to this system, an adult who lacks decision making power can be made a Ward of Court whereby the President of the High Court will make decisions on the said adult's care. This system has its limitations in that it does not provide easy access to immediate decisions regarding day-to-day clinical care. This renders clinicians in Ireland without a legal framework to guide their decisions. In the absence of legal protection, clinicians often resort to making decisions either with the involvement of spouses, relatives, next of kin and appointed carers (Irish Medical Council, 2009). This approach is advised by the Irish Medical Council in the absence of someone who has legal authority over decisions made.

Capacity in clinical practice

In day-to-day clinical practice, issues pertaining to assessing a patient's capacity feature in several different settings. A few examples of scenarios that are commonly encountered are assessing capacity to consent to treatment, assessing testamentary capacity, capacity to manage one's financial affairs and domiciliary arrangements and assessment of one's fitness to plead. The recommended approach to this is always a functional approach. Below is a general guideline on key points that are worth considering when assessing capacity in these scenarios.

Consent to treatment

Consent to treatment refers to one's ability to accept or refuse medical treatment. To illustrate an example: in Liaison Psychiatry, an opinion may be sought by the surgical team on an elderly man with a psychotic depression regarding his capacity to consent to a proposed gastroscopy. Key points to take into account in this setting are:

- The ability to understand and appreciate the information that is relevant to the procedure/proposed treatment.
- The ability to retain the information and repeat it back.
- The ability to understand and appreciate the risks versus benefits of the proposed procedure/treatment.
- The ability to communicate a choice.
- Sequence of decision making should reflect logical consistency.

Fitness to plead

At times a clinician may be called upon to assess a patient's competence to stand trial following a charge. This is a unique setting where a more focused approach in assessing capacity should be utilized. This criteria is based on *Rex v. Prichard* (Prichard, 1836) .

The accused is unfit to stand trial if he cannot fulfil any of the below:

- Understand the nature of the charge.
- Understand the difference between pleading guilty and not guilty.

- Instruct counsel.
- Challenge jurors.
- Follow evidence presented in court.

Testamentary Capacity and capacity to manage one's financial affairs

Testamentary capacity refers to one's ability to make a will. It begins with the presumption that capacity is present. The onus lies on those challenging the will to prove that the testator lacks testamentary capacity. The legal test implies challenger is a disgruntled would-be heir. You must assess whether the person making the will is aware of:

- What a will is and when it comes into effect.
- The extent and value of their property (does not have to be exact but a reasonable idea of the extent is sufficient).
- Who has a reasonable claim to their assets.
- The disposition of assets (who receives what).
- Presence of any psychopathology impacting on this decision.
- Seek collateral where possible to confirm the accuracy of knowledge surrounding assets, reasonable claims and disposition. Family, friends, carers, General Practitioners and previous wills are good sources.

In certain scenarios, especially in later life, the ability to manage one's financial affairs may be compromised due to illness. There are several legal avenues that are present that may help in this regard. However, each avenue has its own limitations. Power of attorney refers to a legal document that allows a person (the donor) to allow another (the attorney) to act in their place on legal decisions usually referring to management of finances and assets. It can be limited to specific situations or general. This terminates if the donor becomes mentally incapacitated and can become a problem as people often do not realise that Power of Attorney will not apply once they become incapacitated.

Another variation of this document is an Enduring Power of Attorney (EPA) that allows an appointed individual to act on an individual's behalf if the individual is mentally incapacitated. A clinician's role is limited to assessing whether the patient:

- Has the mental capacity to understand the EPA
- Understands the effect of creating the EPA
- Does not nominate an unsuitable person as attorney (bankrupts, carers in nursing home/hospital, convicted fraudsters, etc.)

Quite often if an EPA is not secured before a person becomes incapacitated and in the current absence of capacity legislation, appointing someone a Ward of Court is the only avenue for surrogate decision-making. This involves a court-appointed individual/committee to manage the patient's affairs in their best interests. It requires assessments to be conducted by two doctors regarding the individual's mental capacity.

Domiciliary arrangements

In the care of incapacitated individuals, a clinician's opinion may be sought to decide if a patient has the ability to make a decision regarding where they choose to be domicile. This is an important aspect in the care of the elderly where a seemingly simple decision such as where a person chooses to live may in fact be hampered by a cognitive/ physical disability and a lack of clear understanding and appreciation of the nature of their physical and mental health that may impact on their ability to live either independently or with support. Levels of support may range from a few hours a day of home help to the need for full-time care.

As an example, an elderly person with a high risk of falls may in fact be able to choose to live independently but may not truly appreciate the risks and impact should they have a fall. The overall decision should ideally respect a patient's autonomy but also offer objective management of any risks or limitations that may be involved in someone choosing to pursue independent living in the later years of their life.

It is often useful to involve the expertise of members of allied health professionals such as Occupational Therapists, Psychologists and Social Workers that may be able to offer their input to facilitating a person's decision to live independently. Inputs such as optimizing a person's home with ease of access such as ramps, safety alarms and hand-rails could protect from the risk of falling. The consistent assessment of capacity in this regard and efforts to facilitate a patient's decision is fundamental to protect their autonomy and best interests.

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23

Psychiatric Services

Brian O'Shea

'The biggest problem, as always, is money'.(Coid, 1991)

'...psychiatrists should be aware of and concerned with the equitable allocation of health resources'.(World Psychiatric Association, 1996)

'...the major reason why community care has been promoted in psychiatry is that it is considerably cheaper than hospital care'.(Tyrer, 2001)

'The negative voice of experience is often at a disadvantage against the siren voice of hope.(Shephard, 2002)

'Community psychiatry from its inception has been as much an ideology as a scientific endeavour'.(Mechanic, 2001)

'Investment in mental health is an investment that no country, however rich, however poor, can afford not to make'.(Rutz, 2003)

'Populations with high rates of socioeconomic deprivation have the highest need for mental health care, but the lowest access to it'.(Saxena ea, 2007)

'People with psychiatric illness are not like you and me – they are you and me'.(Yawar, 2008a)

Mental health is a costly business (Secretary of State for Health, 1991; Knapp, 2001; Walsh, 2007a; Levinson ea, 2010) and professional mental health workers, service users and families must fight for a fair share of the total health expenditure on behalf of a relatively helpless section of society.(Lancet Global Mental Health Group, 2007) Across the income spectrum, despite often greater disability, mental disorders are often undertreated compared to physical disorders.(Ormel ea, 2008) Promises of better services are often made by politicians as funding continues to fall.(Okasha, 2002; Expert Group on Mental Health Policy, 2006, p. 178; Barry ea, 2008; Walsh, 2009) Closure of large mental hospitals in the US had actually led to increased care costs because of acute admissions.(Rothbard ea, 1998) Ireland has traditionally relied heavily on admission to hospital in the care of people with psychiatric disorder. The fact that over 13% of total Irish psychiatric admissions are aged 65 years and over speaks to the need to further develop old age psychiatry services.(Dixit, 2008) The great majority of persons employed in the modern health service have no immediate role in treatment. Administrative numbers expand with increasing bureaucratisation of health services.

Glossary

Access – ability of person to get a service when required within a reasonable time frame³²¹⁹

Approved centre – treatment/care facility registered pursuant to current mental health legislation and approved by Mental Health Commission (MHC) in Ireland

Choice – retaining control over one's own life, including choice of treatment, access to relevant information, being seen as a participant, and having access to staff and advocates³²²⁰

Clinical governance – a way of improving clinical standards (includes audit, education, R & D, risk management, etc)

Risk – the chance of an event occurring that might impact on objectives of a system

Risk management – aspects of a service directed towards reducing the likelihood of adverse outcomes and managing those that occur

Background³²²¹

³²¹⁹ Alonso ea (2007) estimated that 3.1% of adults in 6 European countries had unmet mental healthcare needs.

³²²⁰ A **mental health advocate** is defined (MHC, 2009c) as someone acting for a psychiatric patient, e.g. advising and defending, or, more widely, involved in planning, delivery and evaluating services.

The move towards the community antedated modern political activity. Most psychiatric patients have been treated outside hospital since the 1950s. The advent of ECT and effective drug therapies provided a strong impetus for communitisation of psychiatric practice. The advent of voluntary admissions increased the expectation of discharges. Other factors promoting discharge included state payments for the unemployed, public housing, and the development of primary care. (Rose, 2001)

The exodus of patients into the community increased re-admissions and pushed total admissions ever upwards. It also influenced number of involuntary admissions, with an upward trend despite less available beds. (O'Doherty, 1998; Hotopf ea, 2000; Muijen ea, 2003, p. 693; Salize & Dressing, 2004) Among EU states during the period 1998-2000 that had available information, involuntary admission rates were highest in Finland at 218/1000,000 of the population³²²². 'Revolving door' and 'new longstay' replaced terms like 'open door'.³²²³ We must achieve a selfless balance to avoid returning to the equivalent of the Victorian buildings that were built when labour and life were relatively cheap. Understimulating hospital environments in the UK (Wing & Brown, 1970) and elsewhere (Oshima ea, 2003) have been found to correlate with institutionalisation. However, an institutional basis for negative symptoms (clinical poverty syndrome) is questioned by findings that such symptoms persist for at least nine years after post-discharge. (Johnstone ea, 1981) This is not to say that psychiatric wards can be very non-stimulating environments³²²⁴. (Goffman, 1991; Radcliffe & Smith, 2007; Yawar, 2008a) Enoch Powell (Minister of Health, UK) told the National Association of Mental Health in 1961 that the following 15 years would see a halving of mental illness inpatient places and the closure of most mental hospitals. Tooth and Brooke (1961) predicted that of all the longstay patients in 1954 none would remain by 1970. They also said that all the needs of the mentally ill (except the mentally retarded) could be provided for with a bed ratio of 180/100,000 population.

Day services

1942 - first day care program established in Russia
 1946 - first program in an English-speaking country starts in Montreal
 1946 - Marlborough Day Hospital opens in London, England
 1947 - Menninger Clinic (Kansas) starts 'day hospital'
 1949 - Yale University sets up similar 'day care clinic'
 1957 - Carse starts the 'Worthing Experiment'; range of services, including domiciliary visits, reduces admissions from Worthing by 59%
 1958 - day care geriatric service starts in Oxford
 1963 - formal US policy of community care dates from *Community Mental Health Centres Act*

British DHSS³²²⁵ recommendations during the 1970s for population of 100,000

50 beds and 25 day places for adult mentally ill
 30-40 beds and 10-20 day places for elderly severely demented
 Local authorities should provide 20-30 hostel places and 60 day centre places for those with social handicaps but not needing continuous medical and nursing care
 Units on a regional or sub-regional basis should be provided for special groups³²²⁶

³²²¹ In 1744, King George II amended the *Vagrancy Act* and ensured the care of lunatics. Private registered homes, wherein the mentally ill discharged from hospital may be placed, were likened to the original private madhouses.

³²²² Followed by Austria, Germany, and Sweden.

³²²³ Revolving door patients show an excess of alcohol and substance misuse as well as non-adherence with prescribed management. (Turner ea, 1999) In fact, a small number of such patients may make up an inordinate percentage of total inpatient length of stay figures. (O'Shea ea, 1996) A 5-year follow-up (2001-5) in Ireland found that severe psychotic illness (hard to avoid) and alcohol-related disorders (despite exhortations to treat in the community) were important causes of re-admission. (Daly ea, 2007a)

³²²⁴ England's mental health wards were criticised in 2008 for having high levels of violence, overcrowding, impersonal care, and for the high numbers of detained patients absconding for days at a time. (Cole, 2008)

³²²⁵ Dept. of Health & Social Services

³²²⁶ Children, adolescents, alcoholics, drug addicts, and secure units.

By 2001 the situation was that provision of secure forensic psychiatry services was uncoordinated, under-provided, and tended to prioritise offender patients and not to support local psychiatric services.(Coid ea, 2001) In Ireland *The Psychiatric Service - Planning for the Future* (1984) set out the requirements of a comprehensive community-based psychiatric service.

Planning for the Future planning norms (Trant Report)

Sector size: 25-30,000

Day care places: 0.75/1,000

Community residential accommodation: 60/100,000

Short to medium stay inpatient places: 0.5/1,000

New longstay inpatient places for < 65s: 0.2/1,000 under 65s

New longstay inpatient places for > 65s: 5/1,000 over 65s

'Ideal' admission rate would to be 5/1,000.

Actual Irish provisions

2001 - 42.5 day hospital places/100,000 in 63 centres (2002 - 32.4) and 92.7 day centre places/100,000 in 104 centres (81.2 in 2002)

3,077 places in 404 community residences (low, medium and high support)(3,136 in 2002)

1987 - 233 community residences (1,625 places)(418 [3,210] in 2003)

Excluding residences exclusively for intellectual disability, there were 1,412 people (M>F, majority with schizophrenia) living in 113 'high support community residences' (rate: 46.6/100,000 population aged at least 16 years) on 31.03.2006.(Doherty ea, 2007)

The recommended number of day care places per 1,000 of the population varies from 0.75 in *Planning for the Future* to 1.88 in Hickey ea (2003) with the Inspector of Mental Hospitals (Department of Health and Children, 2001) recommending 1-1.5.

Hickey ea (2003) recommendations

66 day care places per 35,000 of the population, 11 being day hospital places and 55 being day centre places

There is great variation in the provision of both day hospital and day centre places across Ireland, some areas providing services way below the optimum.(Kelly, 2004) The same observation applies to residential accommodation in the community.(Mulholland, 2010)

3 main obstacles to better mental health (Saxena ea, 2007)

- Scare resources
- Unequal resource distribution
- Inefficient use of resources

A Vision for Change (Expert Group on Mental Health Policy, 2006; see also Anonymous, 2006) makes a number of recommendations: service user/carer involvement in service development/delivery; mental health promotion (enhance and decrease protective and risk factors respectively); establishment of comprehensive community mental health teams (CMHTs); multidisciplinary home-based and assertive outreach services offering a full range of relevant interventions; a recovery orientation; links with primary care and voluntary groups; catchment areas serving 250,000-400,000³²²⁷ run by local mental health catchment area management teams with a national mental health service directorate that works directly

³²²⁷ Regional catchments are required to allow consultant to undertake some degree of special interest work.(see Walsh, 2009)

with the Health Service Executive (HSE); prioritisation of those in greatest need; annual evaluation of services; close all psychiatric hospitals and use the released resources for the new service; local data collection and funding of research; centralised planning and funding of education/training of mental health professionals; the national mental health service directorate should put a plan in place for multi-professional manpower; an implementation review committee to oversee this policy; substantial extra funding adjusted for inflation; and acceptance/implementation of the complete plan. Under a proposed 7-10 year plan, provision of CMHTs should receive priority in order to allow acute beds in psychiatric hospitals are to be phased out.

A Vision for Change (Expert Group on Mental Health Policy, 2006) recommendations

Child and adolescent mental health services - each catchment area to have 6 CMHTs for people up to age 18 years; extra CMHT for paediatric liaison; 1 day hospital/catchment area; nationally, 5 inpatient units of 20 beds apiece

Each adult CMHT for 18-64 year olds/population of 50,000, with 2 consultants (mainly employing home-based treatment); 1 acute inpatient unit of 35 beds and 1 crisis house with 10 places/catchment area; 2 high support intensive care residences (10 places each)/HSE region³²²⁸; 2 pilot early intervention services 'Recovery and rehabilitation' services³²²⁹ for severe/enduring illness: 1 CMHT/100,000 population: assessment, treatment, care assertive outreach, etc; 3 community residences (10 places/100,000); 1-2 day centres (30 places)/300,000; 1 service user-provided support centre/social club/100,000

Older people served by one team/100,000 and 8 inpatient beds; 1 day hospital (25 places)/300,000; unit (30 beds/300,000) for continuing care/challenging behaviour

1 and 2 CMHTs for intellectually disabled children/adolescents and adults/catchment area, respectively
Forensic: 2 teams for children/adolescents nationally³²³⁰ and 1 secure national (adult) unit, and a similarly sized unit for intellectually disabled people who become severely disturbed in context of criminal justice system; court diversion and work with police and other mental health services

Homeless: 2 CMHTs in Dublin, a crisis house (10 beds), local psychiatric acute beds, 2 day centres and 1 day hospital

Substance misuse (i.e. comorbidity of 'a complex or severe substance misuse problem' with mental illness): 1 CMHT/catchment area and expanded services for adolescents

Eating disorders: 4 regional CMHTs and a national tertiary referral centre for children/adolescents

Liaison: 1 team per regional hospital/catchment area (13 nationally)

Neuropsychiatry: 2 national teams (1 unit of 6-10 beds)

Perinatal psychiatric: based in a national maternity hospital

Acute in-patient care based in a regional hospital (50 beds/hospital: 35 for acute adult, 8 for elderly, 5 for intellectual disability, 2 beds for eating disorders)

One 10-bedded crisis house/300,000

4 intensive care rehabilitation units (30 beds in each HSE region³²³¹)

Two 10-place high support intensive care residences/HSE region

One 30-bed continuing care/challenging behaviour unit for elderly

10 rehabilitation beds in approved intellectual disability residential centres

100 beds nationally for 0-18 year olds (5 units of 20 beds each)

10-bed national secure unit for children/adolescents and similar unit for the intellectually disabled

Transinstitutionalisation³²³² refers to the phenomenon of discharged chronic patients ending up in prison or other (unsatisfactory) places. Homelessness has become a major problem in the Western World. Hostels for the homeless may become repositories for unmedicated actively psychotic patients. The fact of being ill

³²²⁸ 4 regions, 8 residences, 80 places nationally.

³²²⁹ See Tedstone Doherty ea.(2007)

³²³⁰ One in a 10-bedded secure unit and one in the community.

³²³¹ The HSE is to create 4 regional health boards by January 2010.

³²³² Or reinstitutionalisation. **Penrose's Law** (after Lionel Penrose who discussed this phenomenon in 1939) = as number of psychiatric inpatients fall, number of prisoners rises. There is some evidence for this in Ireland.(Kelly, 2007) The US saw a 95% decrease in public psychiatric beds since the 1950s and reports from that country suggest that Penrose was correct: vagrancy, crime, imprisonment and neglect.(Weich, 2008)

may have more to do with reported criminality in schizophrenia than any genetic endowment. The move from asylum care has expanded the range of social ills viewed as being 'psychiatric'. (Rose, 2001) It seems probable that many people that once would have been warehoused in psychiatric asylums are now being diverted to forensic units, prisons, and supported housing. (Priebe et al., 2005) Despite there being over 3,000 extramural residential places in the Republic of Ireland, and low provision on the part of local authorities, the Expert Group on Mental Health Policy (2006, p. 253) placed responsibility for shelter on scarce mental health treatment facilities, suggesting that discharged persons who remain homeless be returned to 'their parent service'.

Some of the resistance to decentralising mental health services comes from hospital-bound staff.³²³³ Chlorpromazine became available in 1953. Within two years the population of mental hospital began to fall after rising steadily in most industrial countries for 150 years.

Bed usage (psychiatry)

USA - 450/100,000 in 1955 → 110/100,000 in 1981
 Italy - 210/100,000 in 1970 → 75/100,000 in 1985³²³⁴
 England - peaked at 148,000 in 1954 → 45,000 by 1992 → 42,000 by 1994
 Scotland - 319 inpatients/100,000 in 1985
 Ireland - 930/100,000 in 1999 → 907/100,000³²³⁵

The number of residents in English mental illness and 'mental handicap' hospitals fell from 143,547 and 50,515 respectively in 1954 to 56,900 and 24,909 respectively in 1990. The English hospitalisation rate in 1986 was 128/100,000 and the number of beds was reckoned to be dropping by about 4,000 per annum in early 1993. The Irish hospitalisation rates in 1999 and 2001 were 930 and 907/100,000.

Comparative number of psychiatric beds per 1,000 population (Walsh & Daly, 2004)

	1961	2001
Republic of Ireland	7.3	1.5
Sweden	4.8	0.6
Japan	1.1	2.8

Republic of Ireland v England and Wales 2006³²³⁶ (Walsh, 2007b)

	Inpatients	Rate/100,000	Involuntary admissions
Rep of Ireland	3389	86.5	15%
E & W	32023	52.8	40%

There were 4,321 inpatients in Irish psychiatric facilities in the 2001 census, (Daly & Walsh, 2002, 2003a; cf. also their 2001 publication) a rate of 160.3/100,000 population aged 16 years and over, falls of 78% and 47% from 1963 and 1991 respectively. 3,891 patients resided in such facilities in 2002. (Daly & Walsh, 2003b) In 2001, 55% were male, 38% were at least 65 years old, 69% were single, 17% were involuntary (rate = 26.7/100,000 pop.), 37% had schizophrenia, 18% had depressive states, 14% were intellectually disabled, 54% were longstay (> 1 year) and 36%³²³⁷ were old longstay (> 5 years). High rates were also associated with old age, single male and unskilled worker status. One-quarter of alcohol- and the same fraction of substance-dependence admissions were for less than 7 days, whereas as the same fraction of depressives were in hospital for 1-3 months. There was a large disparity in rates of bed/100,000 in 2001 between different health board areas (range 271.7 in South-Eastern Health Board v 40.0 in South-Western

³²³³ See Saraceno et al. (2007) for a discussion of this and related problems in poorer countries.

³²³⁴ Italy (minus Sicily) has 4,108 public beds (0.78/10,000) and 4,862 private beds (0.94/10,000). (De Girolamo et al., 2007) The Netherlands had 135 beds/100,000 population in 2001. (Weich, 2008)

³²³⁵ People aged 16 and over respectively.

³²³⁶ 53% and 1% of involuntary patients in Ireland during 2007 had admissions lasting less than 21 days and over 1 year respectively. (MHC, 2008)

³²³⁷ Another figure from the same authors is 42%!

Area Health Board). The average length of stay³²³⁸ in 2001 was 26.2 days, the shortest average stay by diagnostic grouping being for alcohol-related conditions (13.7 days); organic psychoses stayed longest (37.1 days – 40.4 days in 2002), followed by schizophrenia (35.6 days). 46%, a quarter, and a fifth of patients with alcohol-related conditions, depression, and schizophrenia were discharged within a week. General hospital psychiatric units developed slowly in Ireland³²³⁹. However, admissions to such units increased from 4.4% of psychiatric admissions in 1991 to 14.2% in 2001. For the first time, 2003 saw admissions to general hospital psychiatric units (44%) surpass those to psychiatric hospitals (38%).(Daly et al, 2004)

General hospital psychiatric units may have problems dealing with disturbed patients (Farnham & James, 2000) and with heavy liaison commitments,(McGennis, 1992) although some of the resistance may come from within the medical profession itself.(Walsh, 1993)

Ireland, traditionally a culture of exodus, is experiencing the influx of foreign ethnic groups in large numbers. Britain, especially its cities, has had to deal with culturally diverse groups presenting with psychiatric difficulties for much longer. Among the reasons cited for such high bed occupancy rates (125% in 1997) in London are concentrations of ethnic minorities with a high incidence of psychosis, unemployment, social isolation and deprivation, and homelessness.

There is a great need to develop readily accessible interpretation services (incl. sign language for the deaf: Du Feu, 2010) in view of the ethnic mix now prevalent in Ireland.(Expert Group on Mental Health Policy, 2006)

Irish Branch of Amnesty International (Amnesty International, 2003) summarised Irish psychiatric services are showing tardy/piecemeal/inadequate/unevenly distributed development with severe under-resourcing in terms of staff, money and available treatments. It urged the Irish government to provide the following:

- Comprehensive, needs-based, service-user led review of services plus full and prompt implementation with due regard to human rights, best practice, and emphasising community care
- Research on needs/services
- Full financial provision
- Necessary resources for MHC
- Effective action on international and Inspector's reports and governmental reviews
- System of personal advocacy and effective complaints procedures (see Health Service Executive, 2005)
- Person-centred service for all in need (emphasis on minorities/children/etc)
- Public education/awareness
- Rights-based legislation

The Irish *Employment Equality Acts* 1998 and 2004 and the *Equal Status Acts* 2000 to 2004 prohibit discrimination on grounds of gender (incl. transsexuality, sexual orientation, pregnancy, maternity leave) or sexual orientation, marital or family status, religion, age, disability, and race.(Equality Authority, 2006)

*Republic of Ireland*³²⁴⁰ *psychiatric in-patient facilities, psychiatric manpower & population*

(a) **Irish Psychiatric in-patient facilities:**

Year	Total inpatients	Total admissions	Comments
1958	21,000		
1963	19,801		
1876	14,473		
1986	11,559	29,392	
1987	10,681	27,743	Alcohol/depression: commonest diagnoses in males/females respectively
1988	9,500	28,432	12% involuntary and 88% voluntary
1989	8,793		National hospitalisation rate of 2.2/1000 pop.

³²³⁸ Excepting patients resident in excess of 12 months.

³²³⁹ The first general hospital psychiatric unit was opened in Waterford (Ardkeen, now Waterford Regional Hospital) under Tom Lynch during the 1960s. By 2006 there were 22 such units in the Republic. The Inspector of Mental Health services emphasised that psychiatric units in general hospitals had still not replaced some large psychiatric hospitals in 2008. Recommendations for such a move date at least to the *Commission of Enquiry on Mental Illness* in 1966 but the idea is much older having been broached by Conolly Norman (1853-1908) of the Richmond Asylum in Dublin in 1904.

³²⁴⁰ It is interesting to note that Ireland came 16th out of 29 countries in Europe, one place ahead of the UK, on the European Health Consumer Index 2007 of public health care system. The Index is based on 27 indicators, e.g. patient rights/information, generosity of public healthcare, and medication access.(Watson, 2007) Top of the list was Austria, with Latvia at the bottom.

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1991	7,500		75% voluntary (not quite the same as informal) ; hospitalisation rate of 2/1,000 (or twice the UK rate)
1992		27,148	Hospitalisation rate of 766.8/100,000
1993		27,005	Married > single women admitted (opposite for males)
1994	5,581	26,687	27% first admissions. Rate of all (first) admission = 753.7 (201.4)/100,000
1996	5,212	26,656	Out-patient clinics at 251 locations/233,512 attendances.
1997		26,069	Admission rate = 959.8/100,000 (all) + 256.8 (first). Depression + alcohol + schizophrenia = 67% all (79% first) admissions.
1998	4,820	25,295	
1999	4,469	25,062	11% of admissions were involuntary. All and first admission rates/100,000 population aged 16 and over = 930.0 and 263.3 respectively.
2000	4,230	24,282	Admission rate = 270/100,000 pop. 16 years and over; 70% of all admissions were re-admissions.
2001	4,321	24,446	Admission rate = 5.7/1,000 pop. of all ages. 70% of admissions = readmissions. Highest rate of admissions in 45-54 year old group. 53% of all and 56% of first admissions were male. Longer stays in private facilities but more readmissions in health board hospitals and general hospital psychiatric units (72%) than in private units (59%). It has been suggested that public sector deals with more severe mental illness (SMI). Schizophrenia admissions = 9%, 20% and 23% to private, general hospital, health board respectively. Unskilled over-represented. 11% involuntary (4%, 10%, and 14% respect. for private, general hospital, and health board facilities). 54% of admissions single marital status.
2002	3,891	23,677	Admission rate = 7.817/1,000 pop. aged 16 and over. 48% of discharges within 2 weeks, 69% of discharges within 1 month, 93% within 3 months. 54% of admissions were single.
2003	3,701	23,031	Highest admission rate was for 45-54 year olds. 33% , 18%, and 16% were for depressive, schizophrenic, and alcoholic disorders respectively. 11% were of admissions were non-voluntary.*
2004	3,556	22,279	56% males, 11% of all and 13% of first admissions were involuntary, 2.5% wards of court; 18% of admissions were to private sector; 54% of all admissions and 52% of first admissions were single; unskilled had highest admission rate, 10 times that for employers and managers; 29%, 20%, 14%, and 12% of admissions respectively were for depression, schizophrenia, alcoholic disorders, and mania.
2005	3,475	21,253	
2006	3,389	20,288	Two-thirds single, 18% married, 7% widowed, 1% divorced; single v married men = 6:1; 22% residents involuntary; 29% inpatients for at least 5 years; highest rate of hospitalisation among 75+ years.
2007		20,769	

*In 2003/4, Ireland had an admission rate of 588/100,000, whilst the rates for England Wales were 298 and 521 respectively; the percentage of admissions that were involuntary for these 3 countries were 10.6, 7.7, and 8.9 respectively; and the percentage of inpatients in hospital for 1-5 years was 1.2 for Ireland and 0.1 for England.(HRB, 2005)

<i>Year</i>	<i>First admissions</i>	<i>All admissions</i>	<i>First as % of all</i>
1965	6,210	15,440	40
1970	7,696	20,342	38
1973	9,018	24,036	38
1975	8,873	25,892	34
1980	8,459	27,098	31
1982	8,702	28,778	30
1985	8,441	29,082	29
1990	7,577	27,765	27
1992	7,443	27,148	27
1993	7,311	27,005	27
1995	7,246	26,440	27
1996	7,130	26,656	27
1997	7,049	26,069	27
1998	7,137	25,295	28
1999	7,105	25,062	28
2000	7,290	24,282	30
2001	7,301	24,446	30
2002	7,060	23,677	30
2003	5,591	23,031	24
2004	6,134	22,279	28

2005 ³²⁴¹	5,917	21,253	28
2006 ³²⁴²	5,601	20,288	28
2007 ³²⁴³	5,853	20,769	28

(b) Irish psychiatric manpower³²⁴⁴

Postgraduate Medical and Dental Board (2002):

The number of senior house officers in 2000 = 205.8.

The number of registrars in 2000 = 142.

The number of approved posts at senior/specialist registrar level on 1/2/2002 = total 30 (general adult, 14; child/adolescence, 7; old age, 4; intellectual disability, 2; and 1 each for substance misuse, forensic, & rehabilitation).

The number of consultant psychiatrists on 1/1/2002 = 261.

Comhairle na nOspideal³²⁴⁵ (2003):

15 additional consultant posts approved in 2002. At 1.1.2003, 276 permanent consultant posts, divided up as follows: 49 in child & adolescent, 5 forensic, 171 in general adult, 30 in intellectual disability, 21 in old age psychiatry – this is not synonymous with filled posts. Consultant/population ratio varied from 1/9808 in East Coast Area Health Board (this includes St John of God private sector) to 1/18154 in North-Eastern Health Board. There were 10 permanent part-time consultants and 60 approved non-permanent consultants. 106 permanent consultants were male (50.24%) and 105 were female (49.76%); no other branch of medicine had such parity, the nearest being pathology (61% males v 39% females) and furthest being surgery (95% v 5%). A total of 25 specialists in psychiatry were in private practice, i.e. not contracted to public hospitals.

Comhairle na nOspideal (2004a):

5 additional consultant posts were approved in 2003. There were 281 permanent consultant posts at 1.1.2004, 227 (49% being male) of them being filled: of filled posts there were 44 in child & adolescent, 4 forensic, 124 in general adult, 23 in intellectual disability, 19 in old age psychiatry. Consultant/population ratio varied from 1/10,360 in Northern Area Health Board to 1/18136 in Southern Health Board. There were 14 permanent part-time consultants and 53 approved non-permanent consultants. A total of 27 specialists in psychiatry were in private practice, i.e. not contracted to public hospitals (all but 4 were in the Eastern Regional Health Authority's three area health boards, 14 being in the South West Area Health Board). The percentage net increases per specialty during 1993-2003 were emergency medicine 292, pathology 81, radiology 72, general medicine 70, paediatrics 68, psychiatry 47, surgery 35, and obstetrics/gynaecology 20; the average increase was 56%.

Comhairle na nOspideal (2004b):

The recommended number of posts were: general adult 1/25,000; special interest [s.i.] liaison 1/500 acute beds; s.i. forensic dependent on PICU development; s.i. rehabilitation 1/100,000; s.i. substance misuse 1/300,000; s.i. psychotherapy 1/medical school; s.i. adult learning disability 1/100,000; s.i. child/adolescent learning disability 1/200,000; child/adolescent 1/50,000; substance abuse depending on local needs; forensic based on development of current service; and old age 1/100,000. One general adult psychiatrist/25,000 is recommended.

Irish College of Psychiatrists (2005)

Funding on mental health services accounted for just 6.8% of the health budget in 2003 [7.3% in 2004 – contrast with England & Wales: 12% in 1998 and 13% in 2003; Department of Health, 2004; 6.6% in 2009], of which 5-10% went on child and adolescent psychiatry even though children under 16 years of age accounted for almost 23% of the population. There are 55 whole-time equivalent (WTE) consultant child and adolescent posts (1 per 16,150 of pop. under 15; the Finnish ratio is 1:6,000) and there are 20 beds (156 recommended)! The College estimated that a comprehensive service for people up to 18 would require 150 WTE posts.

Medical Council (2007)

³²⁴¹ All admissions rate = 701/100,000 aged 16 years or over; first admission rate = 195.4; 72% of admissions were re-admissions; male admissions = 55%; divorced persons had highest admission rate; depressive disorders, 30%; schizophrenia, 20%; alcoholic disorders, 14%; 47% of all discharges within 2 weeks of admission; 49, 32, and 19% of admissions were to general hospital units, psychiatric hospitals, and private hospitals respectively; 62 admissions to children's centres; non-voluntary all v first admissions = 11% v 12%.

³²⁴² All and first admissions rates = 478.5 and 132.1/100,000 population respectively; re-admissions = 72% of all admissions; males = 51% and 55% of all and first admissions; 45-54 and 18-19 years of age highest for all and first admissions respectively; divorced and unskilled overrepresented in all and first admissions; depressive disorders = 29% and 32% of all and first admissions respectively; schizophrenia = 20% and 13% of all and first admissions respectively; and alcoholic disorders = 14% and 15% of all and first admissions respectively (highest in East Wicklow, followed by Roscommon); non-voluntary all v first admissions = 11% v 12% (3% of private hospital admissions were involuntary); 47%, 68%, and 93% of discharges were within 2 weeks, 4 weeks, and 3 months respectively; 2% of discharges were in hospital for at least 12 months; average length of stay = 27.5 days. Half, 32%, and 19% of all admissions were to general hospital psychiatric units, psychiatric hospitals (incl. Dundrum), and private hospitals respectively. 398 admissions (271 for first time) were for persons less than 18 years old. (Daly et al, 2007b)

³²⁴³ All and first admission rates = 489.0 and 138/100,000. Readmissions = 72% of all admissions. Admissions M = F, but rate of all admission higher for F and rate of first admission higher for M. Unsurprisingly the least skilled had the highest rate of admission. Cause of all and first admissions by diagnostic group as %: depressive (28, 31), schizophrenia (19, 12), and alcoholism (13, 14). Involuntary admissions = 11% of all and 10% of first admissions; only 2% of all private admissions were involuntary. 49% of discharges occurred in less than 2 weeks from the admission date. (Daly et al, 2008)

³²⁴⁴ To place matters in world perspective, Nigeria has 1 psychiatrist for over 1.5 million inhabitants. (Gureje & Kola, 2007)

³²⁴⁵ *Comhairle na nOspideal* was replaced by the Consultant Applications Advisory Committee (CAAC) which sat for the first time in October 2009.

Total doctors holding internship registration, 652; total holding full registration, 15,512 (1,367 aged 65 years or more; 12, 394 giving Irish address); 3,798 on register of medical specialists (psychiatry, 313; child & adolescent psychiatry, 74; psychiatry of old age, 34; psychiatry of learning disability, 27).³²⁴⁶

(c) **Population**³²⁴⁷

Year	Total	Males	Females
1901	3,221,823	1,610,085	1,611,738
1961	2,818,341	1,416,549	1,401,792
2002	3,917,203	1,946,164	1,971,039
(2002 65+ yrs	436,001	189,155	246,864)
(2002 25-44 yrs	1,180,259	588,308	591,951)
2006	4,239,848	2,121,171	2,118,677

Discussion

Functions: The emphasis in 'community psychiatry' is on providing a service for a population rather than the traditional focus on patients who come for treatment to a hospital. It is not intended here to describe the basic outline of psychiatric services. Planning of services is required, e.g. resources,(Holloway, 2001; Denihan, 2005) needs,(Slade & Glover, 2001) different requirements of groups of people, liaison with various disciplines, administrators, politicians, clergy, police, and so on. There is a greater emphasis on 'prevention', which often means early recognition of problems. Services should be close to people in need, and must recognise the needs of special groups, e.g. elderly, drug abusers, etc. A multidisciplinary team³²⁴⁸ approach is employed, although considerable gaps remain in filling posts.(Walsh, 2004) What is not needed is the robbing of staff from acute wards to staff the community as happened in the UK.(Samaraskera, 2007) Some services are sectorised³²⁴⁹; some services operate at a district or regional level, e.g. drug abuse or child psychiatry. There is a tension between sectorisation and the need for individual practitioners to gain expertise in defined areas of general adult psychiatry, i.e. sub-specialisation.(Scott, 2002) The hospital may be shared by a number of sectors, collectively a catchment, and used as required. Continuity of care is essential. An exchange of information is needed between different agencies, e.g. GP, general hospital, schools, social services, psychiatrists, psychologists, and community psychiatric nurses (CPNs³²⁵⁰). Privacy of patients must be preserved.(Backlar, 2001) What we write (or store in other ways) has become increasingly important because of freedom of information legislation.

Society requires education about mental health, mental illness, prevention, and services. It is wise to liaise effectively with local and national voluntary groups, e.g. those for schizophrenia, alcoholism, and religious organisations. Too often all that is offered is a 'psychosis only'³²⁵¹ service because of lack of resources and trained personnel in adequate numbers. It is a truism that, despite a widening demand for different services, that even the richest countries are unable to provide for all requests for assistance. A 2002 Irish survey (O'Keane ea, 2004) found that psychiatric clinical resources were not concentrated where they were needed most; rather they were best developed in the wealthiest areas.

Services should ideally be subject to self-audit, research, modification when required, etc. Follow up policies should be crystal clear.

Definitions of resources vary widely. A day centre might provide social activities, company, a cooked meal, possibly a bath and chiropody, but none of the remedial services found in the day hospital. Industrial therapy could be added to this definition.

A day hospital is a building to which patients may come, or be brought, in the morning, where they may spend several hours in therapeutic activity and whence they return subsequently on the same day to their own home or to a hostel. In practice, day hospitals rarely perform as an alternative to acute services, and are more likely to provide rehabilitation for patients discharged from hospital or care and treatment for

³²⁴⁶ For comparison, from specialist register: anaesthesia, 320; clinical genetics, 2; geriatric medicine, 53; neurology, 28; neuropathology, 3; neurosurgery, 16; paediatrics, 182; plastic surgeons, 37; rehabilitation medicine, 9.

³²⁴⁷ Life expectancy in 2001 was 73 yrs for males and 78.5 yrs for females, the lowest in EU; average retirement age from labour force was 63.1 yrs, the highest in EU. Life expectancy in 2009 was 76.8 yrs for males and 81.6 yrs for females, above average in EU.

³²⁴⁸ See *New Ways of Working* in UK: www.newwaysofworking.org.uk.

³²⁴⁹ The best available public system until someone comes up with a better one.

³²⁵⁰ Known under a variety of names, e.g. community mental health nurse (CMHN) or 'psychiatric nurse in the community'.

³²⁵¹ Although psychotic patients **should** be prioritised.(Reed, 1991; Dillner, 1994) The fact that schizophrenic patients are at increased risk of dying alone is troubling.(Nilsson & Lögberg B, 2008)

those cases not viewed as requiring admission. (Burns, 2001) According to Marshall, (2003) day hospitals have been eclipsed to some degree by a vogue for home care, but day hospitals save travelling time and may not carry the same staff safety problems inherent in home visits.

Some barriers to discharge from hospital (e.g. Ishikawa & Okamura, 2008)

Advanced age

Violence (suicide, homicide, and damage to property)

Severe symptoms

Unrealistic understanding of life outside an institution

Financial (inadequate funds or housing)

Wishes of families and community

Note: the MHC (2009a, c) expect that discharge planning start soon after admission³²⁵²

There will always be a small core of patients who need longstay care in hospital. Longstay beds in Irish psychiatric hospitals fell from 11,355 in 1984 to 5,368 in January 1994. Longstay patient accumulation in general hospital psychiatric units became a major problem from the early 1990s with calls for 'hospital hostels' to be built for decanting purposes. The rate of new longstay patient accumulation in 1992 in Ireland was 4 times the UK rate. It has become routine practice now to telephone around asking for the loan of an acute bed.

Stigma has already been discussed. Suffice it to say here that, despite the common belief that tolerance comes with age, it is more often older people who show less tolerance for the mentally ill.

There is increasing pressure from various groups (e.g. MIND) to give patients say in how the mental health services are run. In the USA, community mental health centres, which do not necessarily see the worst cases, have been required by law since 1975 to evaluate the patient's satisfaction with the services.

However, the methodology underlying such reports may be open to debate.

Some recommendations for those involved in community psychiatry (Rowland ea, 1989)

Comprehensive services (adequate range of resources: Trieman ea, 1999)

Continuity of care

Allow wide range of individuals to survive optimally in as normal a situation as possible

Government should have a definite policy and employ a minister (nowadays a 'Tsar') to carry it out

Establish minimum standards

Services from health and social agencies must be integrated

Emphasis must not be on 'discontinuities of location and the run down of hospital beds'

Health services must take continuing responsibility for what happens after discharge

Services for re-admission must be in place

High levels of care and supervision when necessary

Services must be individualised

Consumer, where realistic, should be involved in planning

Assessment and planning should be multi-disciplinary

Avoid creating jobs with conflict of interest (e.g. save money v create resources)

³²⁵² The MHC (2009c) has published guidelines concerning admission, transfer, and discharge to/from approved centres of both voluntary and involuntary patients. Some parts of this document are highlighted hereafter. Proper information exchange between service providers is important in ensuring care both during and after admission. Normally, the patient's consent should be sought. The care/treatment plan should include a risk assessment and a preliminary discharge plan that includes obstacles to discharge, such as homelessness. Approved centres should provide key workers. Admission consent forms conform with good administrative practice but do not obviate the requirement of consent for specific interventions. Entries in case files should be signed with full names, not just initials. Signature banks for everyone (including students) should be maintained and updated. Discharge plans (and summaries) should be comprehensive and include, e.g., follow-up plan and early warning signs of relapse. A comprehensive pre-discharge assessment is advised and those who should know (e.g. the GP) should know as soon as possible that a discharge has occurred. Patients should have somewhere to live before being discharged. They should know what to do if significant problems arise and early appointments should be given to those most at risk. Also, patients should have ample forewarning of discharge. The guidelines suggest that the inspection reports for nursing homes for the last 3 years should be examined before an elder is discharged to such a facility (presumably a role for the social worker). Guidelines (guidance)/codes of practice, whilst not legally binding, can be referred to by Courts or disciplinary hearings.

Do not lose the skills of former hospital staff and develop a skilled community workforce (Sims, 1991)
Make sure that ex-patients have enough money and have the skills to spend it sensibly

Models: There are a number of models for a community psychiatric service of which only three will be mentioned.

Hive System (Peter Tyrer) - hospital is centre of activities

Facilities such as day hospitals and hostels - often containing very ill people (Marshall & Gath, 1992) - and clinics are essential components

Network System (Malcolm Peet) - starts in community and emphasises development of network of community resources involving people with helping skills, both professional and non-professional
Hospitals are a resource but not a dominant one

Matrix Model (Thorncroft & Tansella, 1999) - *geographical* (at country/national, local/catchment, and patient levels – called, 1, 2, 3) and *temporal* (with input, process, and outcome phases – called A, B, C) dimensions

Use these two dimensions to create a 3x3 matrix with 9 cells made of three ‘ACEs’: firstly autonomy, continuity, and effectiveness (principles at national level); secondly accessibility, comprehensiveness, and equity (at local level); and thirdly accountability, co-ordination, and efficiency (at individual patient level)

Ian Falloon in Buckinghamshire hired the few beds that he claimed to need in an affluent community. Supervision registers in Britain must list patients who are at risk for violence, suicide or significant self-neglect. A key worker (usually a CPN) is assigned to every discharged patient. Care Programming infers adequate multidisciplinary assessment of patients and co-ordination of plans by the key worker/care coordinator. The *care programme approach* (CPA) was introduced in Britain³²⁵³ ‘to provide a framework for the care of mentally ill people outside hospital, requiring health and social care authorities to work together’. (Agnew, 2004) It rose over concerns following closure of large psychiatric hospitals. Such concerns included inaccessible, confusing or duplicated services, public safety, and the (overlapping) boundaries between health and social services.

Chief elements of CPA

Systematic assessment of health and social care needs

Agreed care plan

Assignment of named care co-ordinator

Regular reviews where needs are reconsidered and plans are altered as required

CPA has been accused of bringing with it much time-wasting bureaucracy. (Freeman, 1999) Interestingly, a positive association with a case manager in Manchester was associated with a relatively poor outcome (Tattan & Tarrier, 2000) and case-load reduction did not lead to a reduced need for inpatient care in psychosis in another study. (Burns et al., 2002: the age of the patient, prior length of inpatient stay, and recruitment from hospitals did correlate with outcome) As Kingdon and Amanullah (2005) point out, CPA should be monitored to ensure that it delivers what it was intended to deliver³²⁵⁴ rather than act as a ‘Trojan Horse’ to integrate ‘ill-thought through management initiatives and bureaucratisation’.

The centres of major cities, with their high levels of socioeconomic deprivation, represent severe challenges to any model. Rural services, on the other hand, have to contend with greater distances. The major preoccupations of most psychiatrists, often shared by their general medical colleagues, are bed occupancy and shortages³²⁵⁵. Back-up beds for patients who remain too ill or damaged to survive in the

³²⁵³ CPA was introduced in the UK in 1990 and was shown during the mid-1990s to reduce drop-out from care but to dramatically increase time in hospital, probably because admission decisions fell on junior staff more than on multidisciplinary committees. This led to great pressure on beds, particularly in London. (Tyrer & Milner, 2008, p. 165)

³²⁵⁴ Those who need the services most get them.

³²⁵⁵ A retrospective English study of voluntary and involuntary psychiatric admissions between 1996 and 2006 found more involuntary admissions into less public beds; a case mix shift towards psychosis and substance misuse (drastically changing ward milieu), and more involuntary admissions to private facilities. (Keown et al., 2008)

community are fast disappearing.(Dillner, 1994; O'Shea, 1998) Back-up beds are essential to the success of community psychiatry.(Williams ea, 1992) Also, community residential places (of all levels of supervision) have not always kept pace with demand.(Expert Group on Mental Health Policy, 2006, p. 97) It was decided to phase out mixed sex wards (as distinct from units) in Britain in 1997 for reasons of 'safety, privacy, and dignity'. Asylums of the early twentieth century often had separate buildings for both sexes, and the present author witnessed separate hospitals for both sexes in Western Europe during the 1980s.

There often exists an uneasy relationship between psychiatry and justice departments, each redefining the other's territory. Similar tension exists over definitions of who is the responsibility of which sector. Most of this unhappy state of affairs is born of resource considerations rather than from any inherent ill will or any verifiable scientific bank of facts. Illicit drug users present particular problems for security in treatment facilities, as they do in prisons.(Gunn ea, 1991)

GP practice-based psychiatry in Britain has developed unevenly and tends to cluster in those practices with a greater number of partners, training practices, and those running stress, bereavement, or other mental health clinics. While it may reduce clinic referrals there is no evidence that it reduces in-patient numbers. Research in Britain suggests that GPs often want the psychiatric services to continue to look after the psychiatric needs of patients in the longterm, which creates problems for discharge from bulging clinics.(Bamrah ea, 1991; Watters ea, 1994)

Comprehensive home-based care of the seriously mentally ill can be relatively satisfying for both patient and relatives (Wood & Carr, 1998; McLoughlin ea, 2005; Gibbons & Cocoman, 2006) but requires heavy staffing input and there have been occasional tragedies. Withdrawal of such care may lead to loss of gains in the patient and decreased morale in the care team. Catty ea, (2002) in their systematic review, point out that the evidence for home-based treatment of patients is inconclusive because of inadequate descriptions of experimental and control services, the brevity of some studies, and the fact that the nature of others did not allow one to generalise. Johnson ea (2005) have produced somewhat similar conclusions.

Burnout is more common in community-based psychiatrists, particularly within cities, than among those working solely within hospitals.(O'Shea, 1998) The same staff should look after patients whether they be inside or outside hospital. Neglect of this rule may lead to long crisis admissions.(Marks, 1998) Burnout may be quite common in mental health social workers.(Evans ea, 2006)

Recovery model: 'Medicine has come to mean to mend somebody mechanically, rather than to journey with them towards meaning, solace, and harmony'.(Yawar, 2008b) This idea is reminiscent of nineteenth century 'moral therapy'. Alcoholics are said to be 'in recovery' as distinct from 'cured'.(Jacobson & Greenley, 2001) The recovery movement stems from civil rights and disabilities movements³²⁵⁶ and stresses individual experiences (of self and the environment) of the person with a mental disorder, how he/she negotiates a passage through the illness, and the inclusion of attitudes, fears, hopes, and the unique social situation into a comprehensive treatment package. People are inspired by the personal narratives of others who survive significant difficulties. Recovery is never-ending, it is a journey that emphasises the recovery of meaning and value rather than elimination of problems *per se*.(Irish College of Psychiatrists, 2007; MHC, 2008a) The patient wants help to live as full a life as possible. A collaborative rather than prescriptive approach is expected from therapists.(Khan & Murray, 2008; Sugarman ea, 2010) Professionals may worry that adoption of the model may be inappropriate in the face of chronic disorders, amounting in effect to denial, or that it might be employed as an excuse to reduce services. Whilst some suggest that a firm evidence base is required in order to successfully use the model (Schrank & Slade, 2007; Holloway, 2008), there is every justification for tempered optimism applied in an individualised manner.(Roberts & Hollins, 2007) Also, the good doctor will relate to both person and disorder and employ techniques which have the best evidence base.(Mountain & Shah, 2008)

Recovery (MHC, 2005; Irish College of Psychiatrists, 2007)

Individual should not be forgotten in favour of a diagnosis

Treatment and self-management are developed in a collaborative way³²⁵⁷

Optimistic stance is taken

³²⁵⁶ In the US it was promoted by consumer advocacy organisations such as NAMI (National Association of the Mentally Ill).

³²⁵⁷ Psychiatrists may not be very practiced at involving patients in decisions.(Goss ea, 2008)

Support of peers and community resources are identified and used
 Human relationship is fostered between therapist and client
 Service users are involved in service planning³²⁵⁸
 Equality of access to mainstream housing/education/health/social services is ensured
 Wide range of values are addressed in research projects³²⁵⁹ as a balance to 'reductionist' research

Rehabilitation³²⁶⁰ (see also chapter 31)

³²⁵⁸ In a non-scientific (e.g. percentage response not stated) but useful postal questionnaire study carried out by the National Service Users Executive (NSUE, 2009 – info@nsue.ie and www.nsue.ie) 52%, 39% and 9% of respondents respectively were happy, unhappy, and 'maybe' (uncommitted or unsure?) with the mental help service being provided. Patients sometimes feel that they are humoured rather than involved in decisions about their care. The NSUE feel that users may need to represent their own wishes more forcefully or to be accompanied by someone who will advocate for them. Only 59% felt that they were treated with dignity, 34% having the opposite view. Listed 'priorities' for change was headed by 'less medication' but this may have been a self-fulfilling prophesy since it appeared first in a list of possibilities and could be ticked or not (i.e. the answer may have been 'forced'). Interestingly the 'large majority' of members do not have access to the internet, a point that service organisers/providers should keep in mind.

³²⁵⁹ Action research models, psychosocial research, qualitative studies.

³²⁶⁰ The following notes on **rehabilitation** are of a general nature and should be read in conjunction with chapter 31. Early attempts at rehabilitation, as in the York Retreat in England, were nullified by the overcrowding of asylums that followed and the negative institutional values that ensued. (Goffman, 1961) Discharges were much more frequent during the early years of the asylum era than was the case later on. The English charity *The Mental After Care Association (Working for Wellbeing since 2005)* was founded by the chaplain of Colney Hatch Asylum in 1879 to develop ways of supporting discharged patients. Industrial therapy developed after the Second World War. The move to deinstitutionalise the residents of stand-alone psychiatric hospitals has magnified the need to prepare patients, many of whom have no skills or have lost skills, to survive in the wider world with its multiplicity of challenges. In the past there was relatively little attention given to supporting and facilitating daily functioning and social interaction. Treatments often had little impact on daily living, socialization and work opportunities. Patients were marginalised in the same sense that convicts were ostracized. They were often abandoned by their families and were relatively unlikely to be married or cohabitating. There were strong barriers to social exclusion in the shape of stigma and prejudice. Psychiatric rehabilitation work emerged with the aim of helping the community integration and independence of individuals with mental health problems. Quality of life is often poor for people with severe and enduring psychiatric disorders. Their ability to lead meaningful lives is often significantly compromised. Psychiatric rehabilitation (Pratt ea, 2002) is the process of restoration of community functioning and wellbeing of an individual who has a mental disability. Rehabilitation work is undertaken by multi-disciplinary teams and should be evidence-based. Such teams may generalist or specialist or indeed subspecialist (e.g. forensic [Forensic rehabilitation services in particular are underdeveloped in Ireland.] or intellectual disability or head injury: Roberts ea, 2006). Psychiatric rehabilitation seeks to effect environmental change and/or to modify a patient's capacity to cope with the environment. Psychiatric rehabilitation may combine medication, independent living and social skills training (such skills training has not been particularly effective, partly due to poor generalisation: Bebbington ea, 2002), psychological support to patients and their families, housing, vocational rehabilitation, social support and network enhancement, and access to leisure activities. The team should focus on helping patients acquire skills and access necessary resources. Stigma and prejudice are confronted in order to allow social inclusion. The team works collaboratively with patients so that the latter is empowered. The process is person-directed and the plan individualized to the client's unique circumstances. The ultimate aim is full biopsychosocial recovery. Services may include help dealing with government agencies (e.g. benefits), liaising with probation officers and courts, accommodation, supported employment, education, assertive outreach, medication management, family therapy/psychoeducation, coping skills, activities of daily living (ADLs) and help with socialising. Hygiene, which is often poor, requires ongoing intervention. Other issues include sexual health, interpersonal boundary management, budgeting, and advocacy. Physical health is often poor (whether primary or secondary to treatment) and liaison with medical services, especially the GP, must not be neglected. Engagement in more active lifestyles (including sports) should be encouraged. Many clients have disorders that have been unresponsive or poorly responsive to treatment in the past and such interventions must be thoroughly reviewed with the aim of optimising medication (e.g. clozapine) or other (e.g. CBT, cognitive remediation) therapies. Patients may experience problems with understanding or dealing with interpersonal situations (e.g. misreading social cues and not knowing how to respond), prejudicial attitudes or bullying from those who view mental patients as 'different', problems coping with stress (e.g. travel, shopping, using the telephone, or seeking assistance), and poor attention and concentration. Avolition, anergia, and unusual behaviour (responding to hallucinations, mannerisms, and stereotypies) add to the list of energy and motivation. The 'recovery model' (O'Shea, 2009) has assumed central importance in contemporary psychiatric practice. Core components of the model include instilling hope, empowering clients, user-defined goals, a search for meaning, and a clear focus on quality of life. Permeating practice is a willingness to listen to the patient's life story and a reduced emphasis on the psychiatric anamnesis. Longstay patients may have become disillusioned by the low expectations of others, repeated failure, loss of friends and roles, loss of independence and prospects, lack of useful and fulfilling activities, and the passivity of intramural life. 'Recovery' aims to put illness in perspective: this is not a 'schizophrenic' but rather a fellow human who happens to suffer from schizophrenia.

Wing's (1993) social consequences of mental illness

Impairment – direct effect of being ill, e.g. avolition

Disability – problems carrying out ordinary chores

Social handicap – difficulties in performance of social roles and living as one would like to

Personal reaction to having an illness – responses to being ill of self and others

Much of what can be written generally about rehabilitation applies equally to other endeavours in psychiatry. People with mental health difficulties, who should have the same rights and entitlements as are enjoyed by the general population, are more likely to be unemployed, to lose their jobs, and to be in debt than are people with other disabilities. Following a thorough assessment of needs, rehabilitation aims to alter a wide range of personal attributes in order to improve quality of life within the limitations imposed by illness. (Killaspy et al., 2005) Rehabilitation efforts in Ireland have tended to respond to downsizing or closure of large psychiatric stand-alone facilities with 'resettlement' of long stay patients into a variety of community facilities³²⁶¹ with minimal regard to rehabilitation needs. (Irish College of Psychiatrists, 2007) People with severe and enduring mental disorder who were already in the community were little better served. The emphasis was on care rather than self-actualisation (independent living, open employment, own home, education, etc). Whilst antipsychotic drugs improved symptoms much less progress was made in terms of personal, self-care, social, or occupational³²⁶² aspects of their lives. The Irish College of Psychiatrists (2007) adopted the recovery model in order to emphasise a *person-centred approach* (PCA).³²⁶³ Relatives should be included, informed, and supported. Specialised multidisciplinary teams devoted to rehabilitation are essential to effective evaluation and prosecution of rehabilitative efforts.

Stigma/discrimination – how other people view the mentally ill and how they act based on these views

Rehabilitation psychiatry focuses on function rather than symptoms and on assets rather than deficiencies. The patient's understanding of their illness should be elicited. Risk factors for disease (e.g. obesity or smoking), substance misuse, and health screening (blood pressure, serum cholesterol, QTc, cervical smears, mammography, etc) are addressed. A longterm view replaces the shorter vista entertained in acute settings. A continuous process of assessment is necessary. Any positive existing relationships need support and reasonable attempts should be considered to reignite potentially helpful family contacts.

Some useful assessment instruments

Camberwell Assessment of Need (CAN: Slade et al., 1999)

Social Functioning Questionnaire (SFQ: Clifford & Morris, 1983)

Manchester Short Assessment of Quality of Life (MANSA: Priebe et al., 1999)

What the patient can do acts as a starting point in planning activities. The team must acquaint itself with the accommodation history of their client and strive for an understanding of how things might have gone awry. Is the client literate and numerate and does he/she need assistance in handling money? Is basic education or training in novel skills (e.g. computers) required? Does the team need to put in place arrangements that ensure bills are paid in a timely fashion.

The best occupational outcome is the quick return to employment after an episode of illness. Those patients who have been ill or institutionalised over long periods require skilling, re-skilling, training in time-keeping and help with using transport. Volunteer and part-time work may pave the way for full-time work. Many agencies are involved in a tiered approach to training for work and the rehabilitation team should become involved with these organisations (including sitting on management meetings). Some user-led organisations (e.g. the *Clubhouse Model*) have offered supportive employment for people with severe and enduring mental illness. Traditional 'train and place' approaches may not be as effective as 'place and train' methods, i.e. get the job and support the patient in the workplace rather than spending years training for a job that may not even arise.

It is illegal in Ireland (*Employment Equality Act 1998* amended by the *Equality Act 2004*) to discriminate against an employee because of mental health problems.

Risk assessment (and a plan to deal with crises) is a part of rehabilitation just as it is a component of all psychiatric practice. For example, substance misuse or significant sexual vulnerability may influence placement. The 'relapse signature' (early manifestations of relapse) of individual patients should be known to those entrusted with caring or supervisory roles. What medication worked best in the past, how can this be optimised, are side-effects being reported or ignored, and does the patient need prompts to aid compliance? Lauriello and Keith (1997) stress the risk of carers simply being asked to take over from the staff of back-wards of institutions. This negative outcome must be avoided. Adequate support for carers may prevent burnout and disengagement.

A Vision for Change (Expert Group on Mental Health Policy, 2006) recommendations included those for 'recovery and rehabilitation' services for severe and enduring illness. There was to be one Community Mental Health Team/100,000 population. There were to be three community residences (10 places/100,000), 1-2 day centres (30 places)/300,000, and one service user-provided support centre/social club/100,000 population. Rehabilitation psychiatrists are not universal at the time of writing; even less common are full teams.

Rehabilitation psychiatry is a relatively new subspecialty (Irish College of Psychiatrists, 2007) and it behoves psychiatrists practicing in this area to fight their corner for the development and maintenance of services. Practitioners are obliged to audit their work, perform research into process and outcomes, to compare various interventions with one another, to monitor standards, and to be aware of international progress. (Tyrer, 2006)

³²⁶¹ Often they were simply transferred to other similar institutions.

³²⁶² Traditionally, Irish vocational rehabilitation has been divorced from mental health services and has often been too time-pressured for patients.

³²⁶³ PCA involves focusing on the hopes and aims of recovering patients and seeing these as vital aspects of our interventions. Goals defined by the patient define the starting point of the recovery process and should not be overshadowed by the goals of service providers. (Kartalova-O'Doherty & Tedstone Doherty, 2010, p. 46)

Flexible borders are required between general adult psychiatry and the rehabilitation team. The full range of in-patient and community-based residential facilities are required for an effective rehabilitation service. (Kavanagh ea, 2009) It is essential to forge links with employment and housing authorities and voluntary agencies. Funding for the training of professionals should be ring-fenced. Research is required for epidemiology, planning, ensuring service quality and development, pushing staff development, outcome assessment, and economic aspects of rehabilitation.

Innovative rehabilitation in poorer countries is illustrated by Chatterjee ea (2009) who reported a longitudinal study of patients (N = 256, mean follow up = 46 months) who had been ill for an average of eight years with various psychoses (schizophrenia, bipolar disorder, and others) in a rural Indian community. A community-based package was delivered and consisted of medication, psychoeducation, adherence management, psychosocial rehabilitation, and livelihood support. Over 80% engaged with the programme and there were significant reductions in disability. Good outcome was associated with lower baseline disability, family involvement with the programme, medication compliance, and membership in a self-help group. Poor outcome was associated with schizophrenia and not sticking with the programme. The *Camberwell Assessment of Need* (CAN: Slade ea, 1999) consists of a number of questionnaires that assess a wide range of problems³²⁶⁴ experienced by people with severe mental illness. It looks at the perceptions of the patient (service user), his/her carer, and his/her professional worker.

Economics: What is a cost effective strategy in one country and at a particular point in time may not translate to a cost effective strategy in another country or at a different point in time. (Burns, 1999) A 1991 estimate of the annual cost of mental disorder in Britain came to £5 bn, less than a third of which was for direct services. Many homeless psychiatric patients do not apply for benefits. About €1.6 bn per year is spent on disability benefits in Ireland: €640 million (40%) goes on claims for mental illness with the next highest category, musculoskeletal injuries, accounting for 27%. (Baxter, 2004) The relative cost of community versus hospital care has attracted a large but impotent literature. (see Scull, 1977) The provision of hostel and other accommodation rarely seems adequate for the number and variety of those that might benefit from them. Day centres often have to stagger attendances to cope. Homelessness is a major problem among former inmates of psychiatric hospitals, be they patients who stayed for long periods of time in hospital or who are frequently in and out of hospital. Los Angeles has been dubbed America's 'homeless capital'. Rents for private accommodation has tended to spiral beyond the reach of those discharged from hospital. (O'Shea, 1998) There is much bad will between those who want these people treated in hospital under compulsory order and those who see this as a breach of human rights, and this division may be reflected among patients themselves. (Crawford ea, 2004)

Methods of evaluating cost of psychiatric services

Macroanalytic – total system

Microanalytic – part of system, divisible into:

Cost-effectiveness – compare 2 therapies of equal cost for effectiveness

Cost-offset – cost of therapy minus cost saved

Cost-minimisation – compare costs of 2 interventions of equal outcome

Cost-benefit – measuring monetary value of more one outcome

Cost-utility – measuring quality-adjusted life years³²⁶⁵ instead of money

Abconding: Tomison (1989) defined the characteristics of patients who left a psychiatric hospital without announcing, the fact (patients leaving against medical advice or failing to return off leave were not included) as being male, young, involuntary, a discharge diagnosis of schizophrenia, single, many past admissions, longer total length of stay, and police involvement in the admission. Walsh ea (1998) defined absconders as single, involuntary, schizophrenic or personality disordered.

Non-attendance: Why do patients not keep appointments? Factors predictive of this phenomenon are summarised in the table (Mitchell & Selmes, 2007).

³²⁶⁴ It looks at 22 different life areas. There are 3 versions of the CAN: CAN-C or clinical, CAN-R for research, and CANSAS which is a short version.

³²⁶⁵ QUALYS – length + quality of life.

Failure to keep appointments

Youth, poor, non-adherence, uninsured, no address, lack of transport
 Forgot, mistake, ill, lower social desirability, non-secure attachment style
 Demented

Personality disorder, drug abuse, neuroses, unclear diagnosis, lack of insight
 Communication problem between GP and patient, doesn't want to see a psychiatrist or sceptical about psychiatry, poor quality referral letter, long delay before appointment, early treatment stage, poor therapeutic alliance, does not feel involved in making decisions

Carers (Lefley, 2001): Relatives may score higher on scales of anxiety, depression, etc. (Livingston, 1987) than the patients themselves. The reasons for forming relatives' (self-help) groups include information, support, pressure groups for improved facilities (including respite care), therapy for the patients to be given by relatives, therapy for the relative (e.g. stress management), and fund raising for research and resources. Relief admission refers to admission to relief carers during a crisis, whereas respite admission refers to regular, pre-planned breaks from caring. Patient self-advocacy groups are a relatively new phenomenon. The (Irish) Mental Health Act 2001 provides for patients/consumers sitting on the Mental Health Act Commission.

Community treatment orders³²⁶⁶ (CTOs): Bursten (1986) discussed the creation of CTOs whereby treatment at an outpatient department (or back in hospital) after discharge from hospital becomes mandatory. The evidence that CTOs reduce admissions or days in hospital is very limited³²⁶⁷ (Kisely, 2009; Kisely et al., 2007; Kisely & Campbell, 2007; Jethwa & Galappathie, 2008; Hall & Ali, 2009) and Ireland would be wise to wait and see how CTOs perform in Britain before introducing them here. (Walsh, 2010) Tennessee instituted such a policy by statute in 1981 with a subsequent fall in re-admission rates. However, comparison with control groups failed to support the conclusion that these results are due to constraints on outpatients. CTOs are today legally authorised in many American jurisdictions as well as in Australia³²⁶⁸ and New Zealand, (McCall Smith, 2000; Preston et al., 2002; Dawson, 2009) and in England and Wales under the 2007 Act³²⁶⁹. The English *Mental Health (Patients in the Community) Act 1995* allowed the right to remove a patient to a place of treatment wherein the patient could not be given treatment unless he/she so wished! (O'Shea, 1998) Because of this, it was little used in practice. (Taylor & Estroff, 2003, p. 607) Numbers of CTOs under the English *Mental Health Act 2007* exceeded expectations but the infrastructure needed to support compulsory extramural treatment may be less than adequate. (Skuse, 2009) The question of the validity of 'informed consent' from patently disturbed clients is subject to continued debate. Unfortunately, the media is inclined to give rare murders committed by discharged patients (or those lost to

³²⁶⁶ See Dyer (2007) for discussion of the heat surrounding CTOs in the British Parliament and Lawton-Smith et al. (2008) for debate.

³²⁶⁷ The question of the optimal length of hospital stay for patients with psychosis is often driven by economics rather than by clinical considerations. (Capdevielle & Ritchie, 2008) Catts and McGorry (2007, p. 353) are very clear that, at least in Australia, patients on CTOs spend less time in hospital and have less severe symptoms and disability. They also suggest that effective CTOs are those lasting at least 6 months. According to Kisely (2009) of Australia, in terms of numbers needed to treat (NTT) it takes 85 CTOs to prevent one readmission, 27 to prevent an episode of hopelessness, and 238 to prevent an arrest!

³²⁶⁸ Prof Terry Carney of Sydney (2009), a professor of law, stated that Australia uses five times more CTOs per head of population than is used in the US and that these patients are not provided with a second opinion and 'there is no inspectorate'.

³²⁶⁹ *Mental Health Act for England and Wales 2007*, in force from November 2008. This applies only to patients detained in hospital for treatment. If treatment is to be given forcibly the patient must receive such treatment in hospital. Only the Responsible Clinician (RC) (i.e. the Approved Clinician [AC] in charge of that CTO patient) can recall a CTO patient. Recall must be in writing and handed directly to the patient, put through their letter box or posted (first class) to their last known address. Recall does not have to be to the same hospital, or group of hospitals, as manage the CTO. There must be cover arrangements for when the RC is not available. Once a RC has recalled a patient, the patient is AWOL - immediately if the recall note is handed to the patient, at 00.01 the next day if put through the letter box and the next but one working day if posted - and must return to hospital. If anyone interferes with this, S. 128(3) MHA 1983 may come into play: 'Where any person knowingly harbours a patient who is absent without leave or is otherwise at large and liable to be retaken under this Act or gives him any assistance with intent to prevent, hinder or interfere with his being taken into custody or returned to the hospital or other place where he ought to be he shall be guilty of an offence. The penalty is up to two years in prison and/or an unlimited fine.' Once recalled the patient should be assessed and, if appropriate and authorised, treated. This can be undertaken by the RC or by others on his or her behalf. Whether this is the same RC or another one, and, if another one, whether it is an AC from the ward, CRHT or somewhere else is for the protocol to decide. The RC may revoke the CTO such that the patient is again detained (under their previous section unless the patient was transferred to a CTO directly from supervised discharge under the transitional arrangements). This may lead to yet another RC being allocated.

follow up) enormous coverage. Whilst stranger homicides increased in England and Wales between 1967 and 1997, this was not attributable to homicides by mentally ill people. Although there are infamous exceptions, stranger homicides are more likely to be related to alcohol and drug abuse by young males.(Shaw ea, 2004)

Kisely (2009) suggests that a superior approach to orders made in the community is to place a patient on an intervention on leaving hospital, although he admits that research is needed into the long-term effects of such approaches.

Supervision orders have been described (Holloway, 1994) as a bureaucratic solution to inadequate resources and (McCreadie, 2000) as a rod with which to beat psychiatrists should things go wrong. The names of particular patients requiring supervision (violent, suicidal, or self-neglecting) are placed on a special register and close follow up is mandated. Inclusion criteria tend to be vague and such registers present litigation dilemmas for workers – who to include, who to exclude? Despite exhortations, there is little evidence that supervision registers are effective in practice.(Hindler, 1999; Kisely & Campbell, 2007) Neither is there evidence that community care leads to an increase in homicides.(Taylor & Gunn, 1999; Leff, 2001; Simpson ea, 2004) Rose(2001) talks of ‘scare in the community’ (a play on ‘care in the community’)!

Prisons: Concern has been raised over the number of psychiatrically ill and intellectually disabled people in prison. For example, 2% of male and female English prisoners were reported to be psychotic.(Maden ea, 1994)

Seclusion: A small number of patients require therapeutic seclusion.(Gutheil & Shader, 2003) The Irish MHC (2006, 2009e) rules governing seclusion state that it should only be used in the best interests of the patient (not to ameliorate staff shortages) and only if the patient represents an immediate danger to self/others (that cannot be contained by other means). Seclusion must only be initiated by a registered nurse or doctor.(MHC, 2009a) The patient must be told what circumstances will dictate an end to seclusion and he/she must be informed of the termination of a period of seclusion and given the opportunity to discuss the episode with members of the multidisciplinary team. If a patient with capacity refuses to allow staff to inform relatives of the occurrence of seclusion this must be honoured (and documented) unless there are overriding legal or professional considerations. If a patient is subject to 7 or more seclusion orders over 7 consecutive days the Inspector of Mental Health Services must be told of this in writing with reasons given for the practice and details of alternative therapeutic options that were considered. Each approved centre’s policy must state what attempts are to be made to minimise use of seclusion.

If CCTV or other monitoring device is used to monitor patients in seclusion then only designated personnel should be able to view what is shown; it should not be capable of recording or transmitting images (other than the monitoring station); it should not be used if the patient starts to act in a manner which compromises dignity; and it does not replace more direct monitoring of the patient.

Mechanical restraint: Once popular in these islands³²⁷⁰, physical restraint, except in the immediate acute situation whilst something else is being done (talking down, medicating or secluding), is no longer popular. It has been used rather more freely in America. In this author’s view, there is still a need for gentle restraint (‘soft supports’, Posey restraints³²⁷¹) in confused, demented elderly patients who might otherwise need extra medication or suffer fall or other injuries. It also stops injury to others. Common sense, knowledge of local laws and protocols, supervision by senior personnel and inspectorates, and a humanitarian outlook should avoid abuses. The Irish Mental Health Commission (MHC, 2006, 2009d) rules governing mechanical restraint state that it should only be used in the best interests of the patient (not to ameliorate staff shortages) and only if the patient represents an immediate danger to self/others (that cannot be contained by other means).

³²⁷⁰ E.g. during the 1840s, Samuel Hadwin of Lincoln Lunatic Asylum viewed restraint as the very basis of good treatment.

³²⁷¹ Posey Criss-Cross Vests have a circumscribed place in the care of the elderly where a fall could lead to injury. Their use should be strictly supervised and documented and subject to regular review. The ‘V’ neck should face forward. A flat hand should fit between the device and the patient to ensure that it does not interfere with breathing. Pelvic pieces may be required to reduce sliding down. Straps must be secured out of the patient’s reach.

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Cot sides are used to prevent patients falling from their beds. Injuries may result from hitting the head of the sides, climbing over the sides, unlatching the device, or catching the head or neck between the bars. Gaps should not occur between the mattress and the cot side (entrapment hazard), and the mattress (e.g. ripple) should not be high enough to compromise the safety of the cot sides. A risk-benefit assessment should be performed before use and periodically thereafter³²⁷². Use of cot sides and bed rails to prevent injury to the patient does not constitute mechanical restraint within the MHC (2009a) updated rules.

Disaster and military psychiatry

A disaster is severe ecological/psychosocial disruption that overwhelms the coping powers of a population.(WHO, 1992) Modern attempts to understand the psychiatry of disasters date to 1942 and Erich Lindemann's³²⁷³ study of the Coconut Grove fire survivors in Boston. In war zones, debriefing was employed in order to return soldiers to frontline service.

Combat effects may be persistent (Prigerson et al, 2002), e.g. PTSD, depression, occupational difficulties/unemployment, abuse of loved ones/divorce/separation, and substance abuse. Health worries that fail to reach syndromal level are common following combat and other catastrophic events. For example, people may worry excessively about exposure to toxic chemicals. People exposed to warfare or catastrophes may develop psychiatric problems for many reasons: prior coping and functional capacities, previous exposure, sex (e.g. females are more prone to PTSD whilst males are more likely to abuse drugs or act out), leadership offered, unit cohesion and support of buddies, severity and duration of exposure, injury/sexual assault, witnessing death/mutilation/massacres/atrocities, and brain-related factors (CRF, ACTH, catecholamines, and activation of amygdala³²⁷⁴).

The soldier who is subjected to combat-related psychic trauma is helped if he feels safe and properly cared for after removal from the frontline and if he knows that the folks back home care about him. Onerous rotations to frontline service may be damaging. Re-traumatising should be avoided where possible. Society can help to minimise traumatisation by recognising the sacrifices of its soldiers and by not confusing their political beliefs and the efforts of its combatants³²⁷⁵.

Recent large scale catastrophes have included famines, bombings, school campus mass shootings, civil wars, aviation and other-travel related events, flooding, and earthquakes.

Disasters

Natural – hurricanes, conflagrations, flooding, high winds, icebergs, heat waves, etc

Manmade – (a) accidental (e.g. nuclear plant leakage, locomotive derailment)

(b) intentional (e.g. strategic bombing, terrorist attacks)

Planning for disasters must prioritise the meeting of basic needs (e.g. transport, water, food, clothing, shelter, communication with loved ones, acute medical and surgical interventions, monitoring for ongoing threat, provision of accurate information, etc). Communications and delegation aspects require considerable forethought. Services should be so designed as to be capable of expansion as needed. Collaboration and familiarisation with other agencies are prerequisites.(Grant et al, 2008) It should be assumed that existing services may break down. Medico-surgical preparation for such events must include psychiatrists because of (a) the psychological effects of disaster and (b) the experiences of psychiatrists in dealing with strong emotions in victims and tolerating strong personal affect. Psychiatrists should have input into organising appropriate responses to catastrophe. They should employ a wide range of interventions - psychotherapeutic, pharmacological, and group work. Psychiatrists should be prepared to enter affected areas (outreach). Interventions will encompass immediate and longer term involvement of mental health professionals. Friends and relations, witnesses, helpers (including professionals), and direct victims may be traumatised.(Fullerton et al, 2003) Debriefing has not been convincingly demonstrated to prevent PTSD and

³²⁷² The reality is that research data on risk assessment and fall prevention does not necessarily support the efficacy of well intentioned measures.(Cumming et al, 2008)

³²⁷³ Lindemann (1900-1974) was born in Germany and immigrated to the US in 1927. He worked in Boston with Stanley Cobb and Walter Cannon. The Coconut Grove had 1,000 occupants instead of the official limit of 460. The fire, which killed 492 people, seems to have been caused by a flammable methyl chloride leak from a faulty refrigerator. The best known victim was Charles 'Buck' Jones (1891-1942: born Charles Gebhart) a cowboy film star.

³²⁷⁴ Encoding of memories with strong affective loading and instigation of conditioned responses.

³²⁷⁵ E.g. the derision experienced by US soldiers on return from Vietnam.

it may in fact be harmful.(Lilienfeld, 2007) After Action Reports may sustain combatants in the warrior mode and further group identification. They are also an opportunity to identify those who need psychiatric help. CBT and other psychotherapeutic (including group) approaches may be beneficial. Psychiatric patients may miss or stop medication. Some people may experience abstinence syndromes. In such chaotic situations it should be recalled that most people cope³²⁷⁶ with supportive measures (listening, advice, information, normalising experiences, etc) and that what differentiates the normal from the abnormal is the level of incapacity caused as well as the degree of interference with functioning, relating, and employment of coping powers. Services offered should be culture-friendly and the practitioner should not ignore traditional approaches to diversity, e.g. ritual and local healers. Medical services may be over-stretched during warfare or other calamities and trained non-medical personnel may need to be called on.

Conclusions

Community-based services, just like intramural services, vary enormously in quality³²⁷⁷ and resources. Even politicians have occasionally expressed fears that ‘the pendulum has swung too far’ on occasion.(Groves, 1993) There was concern over a British White Paper proposing a broadened definition of mental disorder and the extension of compulsion into the community.(Grounds, 2001 – a Bill before the Westminster Parliament advocating compulsory treatment outside hospital) Priebe and Turner (2003) suggested that there may be a ‘largely unnoticed process’ of re-institutionalisation afoot in the form of an increase in forensic bed numbers in the UK (including in the private sector), increased numbers of compulsory admissions in Europe (inter-country variation is large), a large increase in supportive housing of varying levels of dependence, assertive outreach teams throughout Europe, and early intervention³²⁷⁸ teams. Under the Irish *Housing (Miscellaneous Provisions) Act 2002* local authorities must provide housing to people in their area who require it.

The best asylums provided a wide range of services for the chronic mental patient that are difficult to reproduce extramurally.(Murphy, 1991) The move from vast asylums (Coxe, 1872; Thornicroft, 1992) into the community has brought many challenges with it such as a vastly increased and increasing demand for psychiatric problems from a much wider array of clients than heretofore.(Charlton, 1991; IMJ Editor, 1998; Freeman, 1999; Rose, 2001) Research is constantly reminding us of a vast untouched psychopathology ‘out there’.(Anonymous, 1993) Increasing responsibility (for their own and for others’ work) has been twinned, unfairly, by suspicion of psychiatrists’ motives as mirrored in terms like transparency, accountability and litigation.(Coid, 1994; Turner ea, 1999; Rose, 2001; Tyrer ea, 2001)

St John-Smith ea (2009) stated that novel centralised approaches to public services administration in England diminished the central role of clinicians and the latter have been superseded by audits, targets, and a single remedy for everyone (‘New Ways of Working’). People who know little about psychiatry make the decisions and ‘generic mental health workers’ are tasked with work that they are not qualified to undertake. Instead of a diagnosis, tailored treatment and a therapeutic relationship we now have risk- and needs-assessments, ‘generic psychosocial support’, and isolated groups providing impersonal ‘person-centred services’! Of course, as in other countries, politicians can still send their ill loved ones to the private sector to be seen by a doctor.

A patient sought High Court leave to challenge his committal after such leave had been refused under Section 260 of the 1945 Mental Treatment Act in 2004. The court finding was that Section 260 (granted leave only if the doctor could be shown to have acted in bad faith or without reasonable care) was unconstitutional having regard to Articles 6 and 34 of the Irish Constitution. In Britain the number of unfilled psychiatric posts was a worry,(Storer, 2002; Brockington & Mumford, 2002) as are the posts filled in a temporary capacity in Ireland. Here, as in our neighbouring country, foreign ‘drives’ were undertaken to procure junior doctors and nurses, both of which are in short supply.(Dunne, 1991) Predicting staffing requirements is not a very accurate science. In America there has long been a flight from public psychiatry into the better-paid private sector.

³²⁷⁶ **Resilience** is the capacity to adapt and function despite adversity.

³²⁷⁷ The quality of a service can be viewed in terms of 6 dimensions: safety (no unavoidable morbidity/mortality), equity (equal service for all), effectiveness (no unnecessary suffering), efficiency (no waste), patient centred (clients do not feel helpless), and timeliness (no unavoidable delays).(Bell ea, 2006)

³²⁷⁸ English early intervention teams are often underdeveloped/funded.(Pinfold ea, 2007)

10 guiding rules for re-designing health care in USA (Pincus ea, 2007)

24-hour responsive providing care through a variety of media and in many forms

Meet needs, choices, and preferences

Encourage shared and informed decision-making with patient

Share records and knowledge with patient

Evidence-based approach

Patient safety³²⁷⁹

Transparency

Anticipate need rather than react to events

Use resources in a non-wasteful manner

Co-operate with other clinicians for patient's good

One reason for the use of high doses of neuroleptics may be an attempt to control cases quickly with a view to quicker discharge from a dwindling bed pool.(Dunne, 1991) Tyrer ea (1998) have warned that the development of community psychiatry is useless if one has to look for beds outside the catchment area and that such practice causes disintegration of service delivery. Keogh ea (1999) suggested that there would be no bed problem if there were somewhere to transfer non-acute patients. There is no evidence to suggest that the CPN is any better than the GP at managing non-psychotic disorders and there is much to recommend that the CPN stick to looking after psychotic patients.

Planning using national norms may be inappropriate to local needs. Services need to be designed with the local environment in mind,(Bebbington ea, 2002) e.g. assertive treatment may be more appropriate for areas where services are underdeveloped but less useful in the midst of well-established services.(Tyrer & Milner, 2008, p. 162)

Staff turnover and burnout has correlated with intensity of community work.(e.g. Webb, 1993; Tyrer ea, 2001) High staff to patient ratios (as in the British PRiSM Psychosis Study) and medium-term high-intensity 24-hour input (e.g. in Australia) can produce excellent results in the community that are almost impossible to replicate under cash straitened circumstances.(see Killaspy, 2007) The opposite has also been found, when standard services reduced disability where intensive service failed to do so!(Wykes ea, 1998) Burns (2009) suggests that methodological issues (using treatment as usual instead of head-to-head comparisons) obscure research results in this area and he believes that community mental health teams are a more cost-effective and evidence-based approach than assertive outreach. It is far from clear that intense community-focused care reduces cost or improves clinical status.(Harrison-Read ea, 2002; Tyrer & Milner, 2008, p. 163) Also, standard care may appear inefficient only because of under resourcing.(Bebbington ea, 2002) Priebe ea (2004) looked at assertive outreach and found that weekend working, staff burnout and lack of contact of the patient with other services were independently related to the likelihood of admission, voluntary or involuntary! Craig ea (2004) found a non-significant effect on relapse of assertive outreach over standard care, with only reductions in total number of re-admissions and dropout rates being attributable to the former approach. No firm conclusions could be drawn from this research because of the 'modest sample size'. Johnson ea (2005) used a 24-hour crisis resolution team to augment existing acute services and found that hospital admission was rendered less likely over the ensuing eight weeks; however, compulsory admission rates were not significantly altered. Assertive outreach teams in North East England appear to be reaching the most severe cases (Schneider ea, 2006) but community mental health teams in North London are as effective with such cases as are assertive outreach teams, although the latter may be better at engaging clients and may be better appreciated.(Killaspy, 2006; Killaspy ea, 2009; see Glover ea, 2006) Also, Glover ea (2006) did not find that assertive outreach reduced overall admissions. Whilst Dibben ea (2008) found that a crisis resolution and home treatment team reduced hospital admissions for elderly people but there was no important change in length of stay once in hospital and carers may have been happier with the service than were patients. A Welsh study (Tyrer ea, 2010) found that crisis resolution and home treatment teams reduced voluntary admissions at first but that involuntary admissions increased later on. Bertelsen ea (2008), in Denmark, found that whereas the positive effects of assertive community treatment versus standard care for first episode psychosis waned between two and five years

³²⁷⁹ Most inpatient units in the USA are locked because third-party payers will only release money if the unit reaches standards for the most at-risk cases.(Beck, 2008, p. 923)

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(the assertive approach lasted for the initial 2 years) there may still have been a reduction in hospital bed usage. McCrone ea (2009) reported that a South London crisis resolution team saved money when compared to existing services.

Defining features of assertive community treatment³²⁸⁰ (ACT: Mueser ea, 1998)

- 24/7 coverage
- Direct delivery by a 'multi-disciplinary' team (usually a psychiatrist, a nurse, and at least two case managers)
- Low staff to client ratio of 1:10
- Provision of services at home or at least not in the office
- Caseloads shared across clinicians rather than individual caseloads

Integrated (ACT, programmes for family involvement, and social skills training) treatment was better over two years in reducing psychotic and negative symptoms, substance misuse, non-adherence, and dissatisfaction with treatment than was standard (offer of contact with community mental health centre) in patients with a first episode of schizophrenia spectrum disorder in Denmark.(Petersen ea, 2005) Intensive case-management is best at decreasing hospital use by patients who already use hospitals a lot!(Burns ea, 2007)

In the late 1990s there was talk in Britain of building small hospitals 'in the community' to replace asylums (In Italy, 'residential facilities', catering for very ill people who are rarely moved to independent accommodation, have replaced mental hospitals: De Girolamo ea, 2005). There was also talk of locking up all 'personality disorders'. Hospitals are still collecting 'new long stay' patients such as the young, single male schizophrenic with a history of violence or the middle-aged female with affective disorder or dementia³²⁸¹. New long stay patients, defined as those cases needing longterm inpatient care and refractory to extensive rehabilitatory efforts, were accumulating at a rate of 0.4/100,000/years in England circa 1991. Cognitively damaged patients are particularly difficult to rehabilitate and require high levels of support. In fact, cognitively impaired schizophrenics may deteriorate extramurally.(Wykes, 1994)

There is also a residuum of ageing patients, mostly with organic disorders, who are difficult to place in the community. This was made clear from the TAPS (team for the assessment of psychiatric services – the results of which studies have been generally positive for community living) project in Britain. The cases that were decanted first from institutions tended to do relatively well if their discharge was planned, but the remnant population was much more damaged, i.e. the best cases were picked first. That is why it may be unfair to compare the leavers and the left! The population is getting older and this brings with it increasing levels of chronic morbidity and demands for total care. The mushrooming of nursing homes is paralleled by the increasing use of psychotropic drugs to contain behaviour because of the lack of other feasible alternatives. Psychiatrists are increasingly been ask to do something about elderly patients whose 'depression' or 'paranoia' or disinhibited behaviour is only one aspect of a multiplicity of organic disorders.

Percentage of Irish public health budget spent on psychiatry (e.g. Anonymous, 2004)

Fell by 27.4% between 1971 and 1993 (13.5 to 9.8)

Fell from 8.96% to 7.34% between 1997 and 2004

The MHC (2003):

7% of national health budget went to mental health services

20-30% of health disability is caused by mental ill-health

³²⁸⁰ ACT began in the early 1970s in Dane County (Madison is the county seat), Wisconsin, when Len Stein and Mary Test decided to treat people with serious mental illness in the community. It should be recalled that resources were scare because monies had been diverted into President Kennedy's community mental health centres which catered for the less seriously ill.(Tyrer & Milner, 2008, p. 159) Whilst progress has been made with crisis resolution/home treatment (CRHT) teams in England only 40% of 243 teams were fully established in a survey covering 2005-6.(Onyett ea, 2008)

³²⁸¹ General hospitals will need to increase their resources in order to cope with the rising prevalence of dementia.(Sampson ea, 2009)

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Special care must be taken, and seen to be taken, to make sure that the bulk of mental health funding goes to direct, frontline services. (Thornicroft & Strathdee, 1991; Zinn, 1993) There is great variation in funding in different parts of Ireland (Sheppard & Browne, 2005) and monies awarded should take account of factors such as socio-economic deprivation. Per capita funding in 2005 in the Republic of Ireland ranged from highs of 495.47 for St Brendan's Hospital in Dublin and 323.47 for East Galway through 85 for Wicklow to lows of South Lee in Cork of 53.74 and Kildare of 37.97. Rather than simply taking from better-funded areas, the lesser-funded areas require greater funding.

Survey of Irish psychiatric services (O'Keane ea, 2003)

(1 consultant/each of 32 catchment areas completed questionnaire)

Over-stretched and developed on *ad hoc* basis

Best developed in most affluent areas (negatively correlated with an index of relative deprivation, i.e. medical cardholders)

Limited availability of (sub-) speciality services (e.g. 82% of areas had child psychiatry, 12% had eating disorder services, and 6% had neuropsychiatry)

Quality Framework (MHC, 2007)

Provide holistic, seamless service with full continuum of care provided by multidisciplinary team

Respect and empathy³²⁸²

Empowerment³²⁸³

Good physical environment

Access to services from the community

Families, parents and carers act as part of the team

High quality staff

Systematic evaluation/review of services using best practice

The Lie of the Land (Barry ea, 2008)

Hard-hitting analysis of situation in January 2008: 'asset stripping process'

Attempts to cherry pick parts of Experts' Report for implementation

Asylum lands being given away/sold with no/little financial benefit for psychiatry

Many dilapidated asylum buildings still in use – half of services supplied from such

Some general hospital units outmoded/unsafe

Long-stay patients in dilapidated/deeply impoverished/stigmatising environments

Dwindling relative funding

Fair Deal for Mental Health (RCPsych, 2008)

Funding should meet needs and research

Access to services, especially for most overlooked groups, e.g. adolescence-adult watershed

In-patient services to be improved and locally accessible

Recovery (model) and rehabilitation – especially for chronic illness

Discrimination and stigma – to be tackle everywhere

Engagement with service users and carers – not just at token level

Availability of psychological therapies for all who need them

Linking mental and physical health in practice

The MHC (Finnerty, 2008; MHC, 2008b, 2009b) has expressed concern that staffing of mental health teams has been tardy. The MHC (2009b)³²⁸⁴ reported cuts in already limited community resources and a lack of progress implementing *A Vision for Change*, the need for greater monetary investment by the State (e.g. monies derived from selling of buildings to be spent on community services), a lack of multidisciplinary teams, a need to change clinical work practices (move from institution to community and out-of-hours service provision), best management of resources, and the need to set up a specific Directorate with the HSE to oversee mental health services. The College of Psychiatry of Ireland (Barry & Murphy,

³²⁸² Poor outcomes are associated with patients' perceptions of being ignored or disrespected. (Gordon & Beresin, 2008, p. 3)

³²⁸³ 'Not allowing people to use the abilities that they do have is disempowering in the extreme'. (Brooker, 2008, p. 239)

³²⁸⁴ Within the same report the Inspector of Mental Health Services pointed out that many children are still being admitted to adult settings.

2009) has been critical of the lack of implementation of the recommendations of *A Vision for Change*, e.g. low levels of recruitment of multidisciplinary team members.

Even the best-resourced nations do not reach everyone with a mental illness. Whereas 74% of mentally ill Europeans receive no treatment, the comparable figure for diabetes is only 8%. (Thornicroft, 2007) In fact, unmet need is pervasive and particularly bad in poorer countries. (Wang et al., 2007) Simply providing resources will not ensure that the clinical, as distinct from social, needs of community-based patients are met. (Keogh et al., 2003) Individualised treatment is still essential.

Addresses

Irish Advocacy Network, C/O Health Care Unit, Rooskey, Monaghan. Tel. 047-38918/72863. <http://www.irishadvocacynetwork.com/>
Mental Health Ireland, Mensana House, 6 Adelaide Street, Dun Laoghaire, Dublin. Tel. 01-2841166. <http://www.mentalhealthireland/>

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24

Psychotherapy³²⁸⁵ Brian O'Shea

'Now it is true that what doctors accept into a treatment trial is invariably more exclusive than that which they accept for treatment on a daily basis'. (Clare, 1993)

'...the availability of specialist psychological treatments is not what it should be'. (Nutt ea, 2002)

'The unconscious conflicts of the analysts are now described as hippocampally-based implicit memories and contextual fears by neuroscientists'. (Gorman, 2004)

'One in six people in the UK suffer from depression or anxiety, yet psychological services are almost non-existent'. (Wilkinson, 2007)

'If feelings can be objectified, their power to distress or overwhelm is mitigated'. (Holmes, 2008)

Psychotherapy, in the sense that it is used here, occurs when a person becomes involved in structured interaction with a trained, ethical, licensed individual who endeavours to influence the former's mental state in order to reduce suffering and/or to improve that person's options in terms of psychological function, interpersonal activity, and behavioural repertoire. The aim of all psychotherapy (Ursano ea, 2008, p. 1173) is to help a patient expand his/her range of behaviours and thereby ameliorate symptoms and change patterns that have caused morbidity and that potentially shorten life. Every treatment approach has its devotees and it is important to keep this in mind when evaluating evidence, e.g. Turner (2010, p. 15) was spurred to remark that 'CBY has become almost a panacea'. Historically other treatment approaches have occupied this lofty position, such as psychoanalysis in post-1945 USA.

Psychotherapy can change brain structure and function. The mind and brain are interdependent and neuroimaging shows brain changes after either psychotherapy or physical treatments. However, there may be differences in the direction of change on PET scanning in patients receiving either cognitive behaviour therapy (increased activity in hippocampus and dorsal cingulate gyrus and decreases in cortical activity) or paroxetine (decreased activity in hippocampus and dorsal cingulate gyrus and increases in prefrontal cortical activity) for depression. (Goldapple ea, 2004) Major depressives who responded to cognitive-behaviour therapy (CBT) or venlafaxine showed reduced metabolism in several prefrontal regions on 18F-fluorodeoxyglucose PET scans, although there were additional differences attributable to either modality. (Kennedy ea, 2007) Hippocampal volume was not affected by effective psychotherapy in out-patients with PTSD in a Dutch study. (Lindauer ea, 2005) Functional imaging in patients with social anxiety disorder (Furmark ea, 2002) showed overlap in functional brain changes (blood flow) in patients improving due to CBT or citalopram. Behaviour therapy for anxiety disorders leads to attenuation of abnormalities on brain images in expected areas and activation of regions connected to positive interpretation of stimuli that otherwise lead to anxiety. (Roffman ea, 2005) PET scans with 18F-fluorodeoxyglucose in OCD patients revealed that responders to both medication or behaviour therapy had reduced activity in the right caudate head compared with non-responders. (Baxter ea, 1992) Successful cognitive remediation in schizophrenia may increase activation in fronto-cortical areas on fMRI (Wykes ea, 2002) and *Aplysia*, a simple mollusc, shows neuronal chemical changes when it learns avoidant behaviour and such changes reverse following repeated exposure to the avoided stimulus. (Kandel, 1989)

Despite advances in the neural sciences, people will always need to talk about/out their problems. Some patients simply want to gain greater control over their feelings, even if their symptoms survive, whilst others seek symptom removal. Psychotherapy is not learned from a book (Markowitz, 2003, p. 1219)

³²⁸⁵ The literature contains many studies of psychotherapy on its own or in comparison with other interventions (waiting list, drugs, etc). This chapter will confine itself to general principles.

although knowledge of theoretical frameworks is helpful. Supervision by an experienced and interested therapist offers the best teaching milieu. Greben (1981) defined psychotherapy as any form of treatment strategy wherein a trained individual associates with a person who is looking for help and who, by listening and talking to him, the therapist helps him. He also wrote that 'those who claim special knowledge, who have elaborate rites of passage, who indulge in mystifying private congresses have left the field of psychotherapy and wandered into the field of religion'. Fisk (1993) bemoaned the tendency of psychotherapists to identify with specific schools rather than with the whole field of psychotherapy. Undoubtedly, no matter what the technique employed, the personal skill of the therapist is highly relevant to outcome. The biggest problems with psychotherapy are poor availability (Guthrie & Sensky, 2007, p. 809), a lack of skilled practitioners (Wykes ea, 2005), and the variability of results with therapies like CBT in clinical trials which are probably reflected in clinical practice.(Jacobson & Hollon, 1996)

The trainee³²⁸⁶ must follow up individual cases for long periods and not get entrenched in the conveyor-belt approach to psychiatry. He/she must experience pain born out of the individual interactions with patients, reminders of our own unresolved problems. His/her elders must not take flight into administration or academia, or give the example of defensive hostility towards patients. Personal and clinical maturity comes with time and interaction with real patients, who can be very demanding, as can their relatives. It is advisable to start reading psychotherapy with a broad-based text³²⁸⁷ and to maintain a broad-based interest in the subject until the basic principles are well entrenched. Bloch (1979) suggested that there are 7 factors which indicate a good prognosis in psychotherapy: personality integrated and functioning reasonably, patient motivated to change, expectations are realistic, at least average IQ, non-psychotic, but can suffer from mild personality disorder or a neurosis, strong affect, and life problems not immutable.³²⁸⁸

All of the 'psychotherapies' share three general, if not particular, characteristics. Each has some goal (insight, behaviour change, symptom control, social competence, etc), a technique, (free association, sculpting, video feedback, etc), and a target of intervention (a symptom, family dynamics, interpersonal problems, etc).

Shared functions of different psychotherapies – reestablishment of morale (Frank, 2006)

Combat sense of isolation³²⁸⁹
 Reawaken hopes
 Supply with novel information as basis for cognitive and experiential learning
 Stir emotionally
 Provide experiences of mastery and success
 Encourage application of learned material

³²⁸⁶ O'Shea ea (1983) and Cahill ea (1983) investigated the attitudes of trainee psychiatrists to psychotherapy and the perceived quantity and quality of their training in the art. Their findings were very similar in both the eastern and northern regions of Ireland. They concluded that trainees expressed the wish for supervised exposure to psychotherapy and that their training to date was inadequate. What use they would make of greater exposure and training is debatable. In fact, there is little provision for psychotherapy within various public mental health and managed care services.(Amies, 1996; Power & Gilbody, 2005) Psychotherapy training opportunities seem to have improved in Northern Ireland relative to the Irish Republic and the strongest perceived need appears to be for cognitive-behavioural psychotherapy training.(Rooney & Kelly, 1999) However, uptake of training in Northern Ireland is reported as poor.(McNeill & Ingram, 2009) In 2001 the RCPsych mandated 5 basic psychotherapy requirements for trainees: interview skills, psychotherapeutic formulation, one 12-18 month case using any model, at least 3 cases lasting 12-16 sessions using different models, and some experience of group, couple, family, or systemic therapy. However, Agarwal ea (2007) found that only 9% of SHOs eligible for MRCPsych part II met these requirements and less than one-third of all trainees were aware of the requirements! Provision of psychotherapy by American psychiatrists has declined in favour of drug treatment.(Mojtabai & Olfson, 2008) The best way to ensure trainee training is to make training mandatory.(Denman, 2010)

³²⁸⁷ E.g. Bloch, 2006. Bloch (1986, 2006) supplies a comprehensive reading list and no attempt to will be made to imitate him. A more comprehensive text is Gabbard ea. (2005)

³²⁸⁸ 'Yavis' (young attractive, verbal, intelligent, successful) indicates the desired attributes in a client for psychotherapy in psychoanalysis!

³²⁸⁹ Ward ea (2007) conducted a nationally representative study of 2,711 people aged at least 18 years who lived in private Irish households and found those most willing to disclose distressing information to others were female, younger, and in better mental health.

Assessing a patient for psychotherapy (Roth & Fonagy, 2005; Margison & Brown, 2007; Fonagy, 2010)

Use evidence from literature and from experience

Formulation containing what is unique to this patient (idiographic)

Try to find a 'fit' from good studies, i.e. match patient with a relevant therapy (nomothetic)

Integrative/eclectic psychotherapy (Garfield, 1995)

Very common in practice

Willingness to use approaches that are not viewed as part of the primary treatment, e.g. support during psychoanalysis or cognitive work during supportive psychotherapy

Ventilation infers that the patient confides in others and confesses information about his past and present. Clarification arises from discussion of problems - their nature and relations become clear. Abreaction³²⁹⁰ is the rapid release of emotionally charged material and may be aided by music, deep breathing, and by drugs such as sodium amytal. The repeated ventilation of emotion may desensitise the patient; this is classically seen in mourning (the social expression of grief). 'A problem shared is a problem halved'.

The *therapeutic alliance* is the working relationship that develops between therapist and client when trust has developed between them. It has its origins during infancy and is based on the bond of real trust between the child and his mother. A positive transference³²⁹¹ reaction might take the form of a requirement for the doctor to be omnipotent. This is clearly inappropriate. A negative transference stems from the child's negative emotions, such as fear or mistrust, of his parents. What is required for effective progress is that the patient's 'mature, rational observing ego' combines with the psychiatrist's 'analytic abilities'. (Scheiber, 2003)

Manualised therapies should involve serialised explicit strategies. They are useful for reaching many people who require training in novel treatments. (Mansfield & Addis, 2001)

The functions of the ego include relationships with reality³²⁹², regulation and control of drives, relationships between the self³²⁹³ and others, defence of the self, synthesis³²⁹⁴, cognition, and autonomy.

The chief types of client who are suitable to psychotherapy are 'neurotics'³²⁹⁵ and some patients with personality disorders or psychosomatic conditions. Guided mourning in cases of abnormal grief reactions is a good example of how the act of focusing attention on a problem may facilitate natural healing processes.

The traumatic experience of being psychotic or being related to someone with psychosis requires psychotherapeutic intervention to assist in coping and adaptation. (Holmes, 1991) Psychotherapy, at the very least, improves compliance with medication, (Pampallona ea, 2004; Miklowitz, 2008) although this is by no means a universal explanation of how it works, (Tarrrier ea, 2004) and, at least in regard to treating depression, client preference for psychotherapy or medication may, at least partly, determine choice of intervention. (De Jonghe ea, 2004; Olofinjana & Taylor, 2005) The main predictors of compliance with psychotherapy for depression in a study conducted by Ayuso-Mateos ea (2007) were social support and previous use of social or health services.

The *Balint technique* (Balint, 1964) is based on psychoanalysis but has been adapted for general practitioners. A more eclectic technique is favoured today. The *systems approach* was discussed earlier in the book.

Psychotherapy on the internet/computer-assisted therapy. There is increasing use of psychotherapy by computer (or books - bibliotherapy) rather than by live therapist. (Christensen, 2007; Spek ea, 2008) Marks ea (2007) list reduced waiting lists,

³²⁹⁰ There are attempts being made to use LSD again in therapy, albeit under stronger controls. (Morris, 2008)

³²⁹¹ I agree with Browne (2008, p. 268) that much of what psychoanalysts would say arises from the subconscious past during transference is in fact derived from here and now, real evoked feelings. True transference and countertransference are *unreasonable*. (Nurcombe & Ebert, 2008, p. 53)

³²⁹² Adaptive, reality testing, and maintenance of a sense of reality.

³²⁹³ The modern name for ego is self.

³²⁹⁴ Able to hold together as an individual.

³²⁹⁵ Although obsessionals may incorporate intellectual insights into their obsessional thinking, rather than benefiting from them.

increased convenience and confidentiality, and lessened stigma, as advantages of this technique. Christensen ea (2004) recruited people with depressive symptoms by survey and assigned them to a cognitive behavioural therapy website or an information website or to an attention placebo condition: only both of the former approaches reduced symptom levels; the authors point out that sustainability of results require testing and that drop out rates can be a problem (do completers differ from non-completers?). Nevertheless, computer-assisted cognitive therapy reduces the need for therapist contact,(Wright ea, 2005) although some contact with a live therapist seems to be important.(Baer & Greist, 1997; Spek ea, 2007; Schmidt ea, 2008; de Graaf ea, 2009) According to Christensen ea (2006), brief online CBT for depression is inferior to extended interventions (but see Mackinnon ea,2008, for an opposite opinion), but longer programs lead to more dropouts. Systematic reviews (Kaltenthaler ea, 2008a,b) found some evidence for the effectiveness of computerised CBT for depression but noted high drop-out rates in one review and rates comparable to other forms of treatment in another review and little consideration of patient preference or treatment acceptability as well as a lack of information on how cases were recruited. Another systematic review (Waller & Gilbody, 2009) noted the high drop-out rates and the need for considerable support of clients from staff as well as the interesting finding that clients looked more favourably on computerised CBT than did therapists! Carlbring ea (2007) found internet-delivered CBT for social phobia better than being on a waiting list. Computer-assisted cognitive remediation exercises show promise in the amelioration of the cognitive effects of depression (Elgamal ea, 2007) although the benefits in schizophrenia may be less certain.(Dickinson, 2010) Computer-assisted CBT may broaden its availability for the adjunctive treatment of substance dependence.(Carroll ea, 2008) Brief computer-based interventions have not been shown to be effective for alcohol-use disorders.(Maio ea, 2005)

Virtual reality exposure. Computer-generated video simulation offers a practical approach to real world fears , e.g. fear of heights, spiders, or flying.(Maltby ea, 2002)

Telephone-administered psychotherapy. Mohr ea (2005) found that depressed patients improved significantly during 16 weeks of telephone-administered CBT. Lovell ea (2006) reported equal effectiveness for exposure and response prevention for OCD given telephonically or face to face.

Counselling³²⁹⁶ is a relatively superficial intervention. It may be non-directive³²⁹⁷ or directive.³²⁹⁸ Specific advice or assistance may be offered and self-help materials may be recommended. Few GPs have the time to do much in the way of formal counselling so they may wish to employ a counsellor. Practice nurses could be trained to counsel patients with mild mood disorders. Indeed, primary care-based counselling was as effective as cognitive therapy for depression.(Ward ea, 2000)

Crisis intervention is associated with Lindemann and Caplan. It aims at limited but definite changes in the way one deals with distressing situations. It is short in duration and is based on the assumption that out of the flexibility that is created by chaos may come improved functioning if guidance is given at the right time.

³²⁹⁶ A rash of 'counselling' in recent years has led to a strong call for qualifications and a system of accreditation.(Okasha, 2002)

³²⁹⁷ Client controls session content; counsellor listens and responds in a warm and supportive fashion, and tries to understand problems and ask appropriate questions.

³²⁹⁸ In directive counselling, specific sources of distress in the patient's circumstances are identified and encouragement is given to directly tackle problems or to make lifestyle changes.

Existential psychotherapy looks at the ways we deal with fundamental issues of living, e.g. the concept of freedom. An increased self-awareness is seen as being of greater importance than any delving into the unconscious mind.

Group therapies (O'Shea, ea, 1984) had their beginnings in tuberculosis sanatoria (Pratt, 1907). Joseph Henry Pratt³²⁹⁹ found that if patients confessed to others in a group and received inspiration from the other group members that their health improved. The group becomes the external world in microcosm, albeit a world in which evoked thoughts and feelings can be safely explored. The aim is to nurture insight and strength that are then used in the real world. Many varieties of group therapy have evolved since then. Groups may be 'open' or 'closed' depending on whether new members are allowed in or not after the sessions have started. The average group has about eight members, meets weekly for sessions lasting about an hour, and continues for one to two years.

Small group³³⁰⁰ psychotherapy

Cohesiveness - members feel that they belong to the group

Interpersonal learning - learn from others' experiences

Altruism - hope is won back by being valued and helped by others

Modelling - learn from others' reactions to oneself, and copying of others' behaviour

Universality - others have similar problems

Catharsis - opportunity to express strong emotions³³⁰¹

Characteristics found in a group

Common experience (or disability) of members

Mutual help and support

Reinforcement of self-concepts of normality

Collective willpower and belief - looking to other members for validation of their feelings and attitudes

Promotion of factual over intrapsychic understanding of personal problems

Action-orientated - members learn by doing and are changed by doing

Confidentiality is essential if members of a group are to feel confident about opening up and confessing to others.

Group therapy has expanded into the wider areas of self-help groups such as weight-watchers, groups for relatives of patients with psychoses, and skill-learning groups.

It is difficult to design a randomised control trial of therapy in mixed groups.

Encounter groups³³⁰²: 8-16 participants take part, making it bigger than small group therapy groups.

Personal growth is the aim. Emphasis is placed on frank expression and honesty. The group leader promotes closeness, interaction, cohesion, a sense of belonging, and mutual concern. Group meetings may be once off (e.g. marathon group) or held more frequently.

Psychodrama (Jacob Moreno) attempts to help participants through role-play. Conflicts are re-enacted in a group format. The patient/protagonist selects other group members/auxiliaries to adopt roles (parent, sibling, etc) to allow him to relive relevant past/current conflict-laden situations. A fellow group member may act as alter ego (i.e. act the part of the patient) in order to explore communication and divine better coping mechanisms. There is emotion release and learning

Supportive³³⁰³ psychotherapy, an often-undervalued intervention (Ursano & Silberman, 2003, p. 1197; Grant, 2007, p. 114) and rarely taught skill, remains the most commonly practiced form of psychotherapy in psychiatric practice. (Tanielian ea, 2001; Winston, 2008, p. 1257) Support is an integral part of all psychotherapies and most schools practice supportive strategies at various points in the course of therapy. It may be specific for certain disorders, e.g. psychoses or borderline personality disorder. From an analytical

³²⁹⁹ Pratt, an Internist at Massachusetts General Hospital, gathered TB patients at the Boston Dispensary for weekly discussion groups and found that such groups offered mutual support and diminished levels of depression and isolation.

³³⁰⁰ As distinct from therapeutic communities.

³³⁰¹ Excessive intellectualising can be confronted by the group to the benefit of members who have 'insight' without feelings, i.e. those using *isolation of affect*. This may be easier to achieve in a group than in individual therapy.

³³⁰² These were started by Carl Rogers, (Lieberman ea, 1973) who also invented client-centred/Rogsonian therapy.

³³⁰³ L. *supportare*, to carry.

perspective, suitability includes poor reality testing, poor impulse control, poor interpersonal relations, inability to sublimate, poor balance of affects, and poor verbal facility. These are seen as symptoms of ego deficits. Supportive therapy is not as glamorous as the so-called 'brief therapies' (in fact, most therapies are brief because of dropouts and clinical improvement – Levenson et al., 2000), offspring of psychoanalysis. Defences are shored up rather than broken down. The therapist adopts the role of auxiliary ego for the patient. Techniques include suggestion, reassurance, reinforcement, advice, reality testing, cognitive restructuring, clarification, limit setting, environmental interventions, and current use of medications. 'Lending ego' refers to the modelling of mature behaviour by the therapist. Interventions are tailored to suit the patient (flexibility). The material dealt with resides close to the patient's awareness.

Nidotherapy³³⁰⁴ is a systematic attempt to change the environment (which may precipitate relapses) rather than the patient in cases where the latter is unable to change (older readers will remember the term 'environmental manipulation'). It tries to develop an 'adaptive fit' between person, who if well informed should decide their needs, and environment. Motivation to change is unnecessary. (Tyrer et al., 2007) Evidence of efficacy is limited to case reports. (Tyrer, 2002)

The psychoanalytic family of psychotherapies: Therapy duration has become progressively shorter over the years and more focused on current problems, and has shown a trend away from the old *tabula rasa* (blank screen³³⁰⁵) approach that invited transference to a greater and more open involvement by the therapist. Transference is perhaps the same as (or similar to) the behaviourist's notion of generalisation.

Selected prominent figures from history of psychoanalysis

Sigmund Schlomo Freud (1856-1939), founder of psychoanalysis, neurologist, born in Freiburg (now Příbor) in Moravia, parents Jacob Freud and Amalia Natanson. His half-brother Philip made Amalia pregnant, which possibly influenced Oedipus complex³³⁰⁶ idea. A refugee of the Third Reich himself, four of Freud's five sisters died in Nazi camps. Early on, Freud published neurological and neuroanatomical works, including a monograph on aphasia that Erwin Stengel (1902-1973) translated into English in 1953. Married Martha Bernays, studied under Charcot and published, with Josef Breuer (1842-1925: of reflex fame) *Studies on Hysteria* in 1895. Possibly addicted to cocaine; his colleague, Carl Koller (1857-1944), discovered its local anaesthetic properties. In 1894 and 1899, he had nervous breakdowns. During this period, immortalised in *Traumdeutung* (1900), Freud corresponded with Wilhelm Fliess, inventor of the concept of a nasal reflex neurosis. Freud analysed himself, so starting a family of analysts, and each member thereafter being analysed by someone who was analysed by someone else. Claims for cures criticised in recent years, with talk of former patients dying in mental hospitals. He provided a framework allowing the conceptualisation of mental processes where there had previously been only demonology and degeneracy. Mapother believed that Freud was more of an artist than scientist. Freud may have got major ideas from the German philosopher Friedrich Nietzsche (1844-1900). Merskey attacked Freud's idea of 'repression', believing that it has been used unethically to produce false memories of sexual abuse in infancy. Suffered from carcinoma of maxilla and palate from 1923 and received repeated surgery and radiotherapy. On September 23, 1939 in London, his physician and friend Max Schur administered an overdose of morphine at Freud's request.

Bertha or Elsa Pappenheim (Anna O) (1859-1936) is the best known patient of Freud and Breuer. Lessons learned during her treatment were used in the writing of *Studies on Hysteria*. She would later become interested in separation anxiety. Merskey argues she had a depressive disorder, morphine and chloral hydrate dependence, hysterical conversion, and cyclothymia! Other patients of Freud included Ida Bauer (*Dora*) and Sergej Pankejeff (*Wolf Man*).

Anna Freud CBE, (1891-1982), a school teacher and child analyst, was Freud's youngest child and closest disciple. She observed children at play, was analysed by her father, had no medical qualification, and remained a spinster. Her main contribution was *The Ego and the Mechanisms of Defence*, developed from her father's work.

Carl Gustav Jung, (1875-1961) leader of the school of 'analytical psychology', student of Janet, and a pastor's son, was born in Switzerland and worked with Bleuler at Zurich. Jung corresponded with Freud from 1906 and met him in Vienna a year later. From 1908 to 1914 he was Freud's closest disciple. Jung was concerned with the inner world of fantasy and with interpreting unconscious material in dreams and artistic production. He propounded three levels of psyche: conscious (including persona – outer crust of personality), a 'personal unconscious', containing unique drives and memories, and 'collective unconscious', an inherited, deeper level composed of collected ancestral memories: we are programmed to act in archetypal ways (e.g. the 'hero'). Well-known archetypes (ancient stereotypes) include the 'persona', our social mask, the 'anima', the inner soul-self that is in touch with the unconscious, and the male counterpart of the anima, the 'animus', and the 'shadow', the latter containing unconscious tendencies that must be 'revealed' in therapy. A 'complex' consists of a group of interconnected ideas that arouse feeling and influence action. Jung wrote about 'introversion' and 'extraversion', whereby libido is directed inward or outward. The 'Self's' objective is to maintain an integrated, stable personality. 'Individuation' is the struggle for self-realisation, this process being disturbed in neurosis.

³³⁰⁴ L. nidus, nest.

³³⁰⁵ The 'therapeutic frame' refers to the relative anonymity of the therapist, the fact that sessions are held for a specified time in a specified place, and the fact that meetings outside session time are the subject of exploration within sessions.

³³⁰⁶ A 'triangular' complex, which includes the preoccupations of boys and girls with both parents, has been suggested to replace the Oedipus complex. In reality, many people do not remember much about this phase in their life because it did not cause much upset at the time.

Karen Horney (1855-1952), a native of Hamburg, rejected Freud's 'penis envy' and blamed woman's inhibition on the strictness of her upbringing, i.e. women have sexual problems because of social circumstances not because of biology; she believed that aggression is learned, not inborn.

Melanie Klein (1882-1960) worked with pre-oedipal children using play analysis and she placed the Oedipus complex in infancy! Objects, for the infant, are good or bad; part is confused with whole: breast is equated with mother. At about six months the baby is biting objects (oral sadistic stage) and fears mother will punish him for this hostility. Through denial and projection (attributes of self are imagined to belong to others) the infant assumes a 'paranoid position'³³⁰⁷. Ambivalence towards objects may lead to guilt and a 'depressed position'³³⁰⁸. Klein's 'projective identification' (subject projects part of self onto object, then identifies with object or elicits response in object corresponding to qualities of the projection) was further developed by Wilfred Bion (1897-1979). Klein's first 'patient' was her own daughter, Melitta Schmideberg, who later became an analyst working with delinquent adolescents and who resented her own mother's intrusions so early in life!

Alfred Adler (1870-1937) was born in Vienna, had rickets as a child, trained as an eye specialist, converted to Christianity from Judaism, and died at Aberdeen. He met Freud eight years before Jung. He later broke with Freud, rejected libido theory, founded 'individual psychology', and taught that contemporary environmental factors were more important than sex in determining human behaviour. Adler tried to understand how an individual arrived at his present life-style. Current problems were given due attention in therapy. According to Adler, we all have an 'inferiority complex' and compensate for this via the 'masculine protest'.

Harry Stack Sullivan, (1892-1949) stressed interpersonal dynamics and defined personality in terms of relative and enduring patterns of recurring interpersonal behaviour. Sexual problems are but one aspect of a person's difficulties. Treatment should be centred on the patient-therapist relationship. Sullivan discussed everyday events with his clients and used pointed questions and provocative statements in preference to theory-based interpretations. A homosexual himself, Sullivan believed that patients need a same-sexed therapist.

Helene Deutsch (1884-1982) wrote *The Psychology of Women* and challenged Freud's dictum that the 'enigma of the female' could not be understood by either sex.

Psychoanalysis was the child of S B Freud (see boxes). Freud identified dreams³³⁰⁹, slips of the tongue, and free associations as important windows on the influence of childhood and the present conflicts of the patient. The goal was to elucidate the 'childhood neurosis' as presented in the transference neurosis. Therapy focuses on the recovery of early experiences as they appear in the patient-therapist relationship. The transference neurosis, as distinct from transference phenomena, is the sustained appearance of the transference over time. The patient experiences the analyst as he/she once did an earlier significant figure. The analyst avoids gratifying wishes (abstinence – avoids becoming a figure from the past in reality) and does not take sides in the patient's conflicts (neutrality). Such stances assist in the emergence of the transference³³¹⁰. Classically, countertransference is the analyst's response to the client (modern analysts admit that some responses are 'normal' or non-neurotic). Resistance (experienced by the analyst) derives from the client's defences and may lead to the break down of free association³³¹¹. Interpretations, often given piecemeal, involve the linking together of the patient's experience of an event with the transference experience of the analyst and the significant figures from childhood. Many analysts wait until material is very close to consciousness (or is a symptom of resistance) before offering interpretations (unless it is 'trial interpretation' during an assessment for analysis). Too early interpretation may make the patient feel that the analyst is lost in his own theoretical world and hadn't been concentrating on his client. Shorter (focused) psychodynamic treatments necessitate earlier interpretation than is the case for open-ended analysis. Unless resistance is addressed early time-limited therapy will founder. (Gabbard & Nittler, 2008, p. 672)

Some psychoanalytic ideas

Instincts (drives): The frontier between the mind and body; the physical representative of stimuli coming from within the organism and reaching the mind; and a measure of the demand made upon the mind for work because of its connection with the body. (Freud, 1915) Inner pressure builds up within the person from a source in a bodily stimulus (e.g. mouth, anus, phallus) and the instinct is used to eliminate this pressure through another person (e.g. sexual activity). Freud's first instinctual theory opposed sexual and self-

³³⁰⁷ Good and bad aspects of the mother are split. The internalised good aspect is threatened by the externalised bad aspect. The results are fear, rage, and hatred.

³³⁰⁸ The child realises that mother has both good and bad aspects and so comes to fear that she, the loved one, will be destroyed by the child's hatred.

³³⁰⁹ Freud described dreams as the 'royal road to the unconscious' whereas Beck described emotion as the 'royal road to cognition'.

³³¹⁰ According to Melanie Klein, transference is not just a re-run of past relationships, but also derives from current intrapsychic relational patterns.

³³¹¹ Counter-resistance refers to the impedance of therapy by psychological processes in the analyst.

preservative instincts. His final instinctual theory opposed the controversial death instincts (Thanatos) which he saw as tending towards destruction of the life instincts (Eros: sexual and self-preservative instincts).

Personality development: Freud described child development as passing through psychosexual stages. During the oral stage the erogenous zones (skin or mucous membranes possess the capacity to sexually arouse³³¹²) are mouth, lips and tongue. This stage lasts until about 18 months when the major source of conflict revolves around feeding, the latter providing a major focus for the relationship between mother and child. It is very important for a mother to tune into her child. Erickson defined a developmental crisis at this stage of basic trust versus mistrust. The anal stage lasts from approximately 1 to 3 years, conflict being focussed on toilet training with major issues over power and control between parent and child (Erickson's autonomy versus shame and doubt). The phallic stage centres on penis and clitoris (about 3–5 years of age) with the main issue being the Oedipus complex. The boy wishes to possess his mother physically in a manner derived from his observations/intuitions about sexual life and he tries to seduce her by proudly showing her his penis. (Freud, 1940) He wants to supplant father in mother life. He is scared that his longings will lead to loss of paternal love and protection. He imagines that girls once had a penis and lost it as a punishment and worries lest the same will become him as punishment for his desires. As a consequence, castration anxiety³³¹³ and abandonment of oedipal wishes follow and he identifies with his father and wants to be like his father rather than to usurp him. (Erickson's stage: initiative versus guilt). A latency period follows (about 5-12 years) when sexual impulses tend to become repressed (controversial). (Erickson: industry versus inferiority). The child applies himself to his education. The final stage is the genital one wherein penis and vagina constitute erogenous zones (achieved at adulthood). Heterosexual relationships, love, affection, the development of a secure identity and a capacity for intimacy are of major import as is adapting to the values and expectations of society. Fixation develops when excess libido (psychic energy) remains at one of the earlier stages: this may arise from deprivation or over-indulgence, e.g. anal fixation (obsessional personality with excess orderliness, retentiveness and obstinacy). Regression occurs when there is a return of libido to an earlier stage.

Model of mind: Freud divided the mind into conscious, preconscious and unconscious parts. Consciousness is a highly transient state. (Freud, 1940) and the preconscious can become conscious relatively easily. Strong censorship resides between unconscious and preconscious. The contents of the unconscious are instinctual. (La Planche & Pontalis, 1973) The form of thinking in the unconscious is known as primary process thinking: opposites occupy the same time space, related concepts are condensed into unity, fractions of ideas represent whole ideas., sense of time is absent, the pleasure principle predominates, and there is indifference to reality. Rendering the unconscious conscious is the goal of treatment.

Structural model

The primary process, the pleasure principle and wish fulfilment are aspects of the **Id**.

The **Ego** has conscious, preconscious and unconscious components. It can adapt to reality (*reality principle* allows for a delay of discharge of impulses until a suitable object can be found). Secondary process thinking (rational, capable of solving problems and self-protective) replaces primary process thinking. The Ego reconciles demands of the Super Ego and Id. The Ego has a variety of defence mechanisms that come into play in response to anxiety.

The **Super-Ego's** role is judicial in nature. Freud attributed three functions, to the Super Ego: conscience, self-observation, and the formation of ideals. The Super Ego is heir to the Oedipus complex and is set up by internalising parental prohibitions, ideas and values. Classically it develops about 3 – 5 years of age, whilst Melanie Klein described its development at an earlier stage (supported by observation). Through the Super Ego, the child internalises social (parental) standards.

Concepts

Treatment Alliance is the non-neurotic, rational, reasonable rapport that the client has with the analyst. It allows him to work purposefully in analysis. The patient has to want treatment and has to harbour basic trust and a capacity to deal with the frustration and the rigours of treatment.

In the **transference** the client unconsciously displaces behaviours/feelings from childhood figures onto the analyst. He re-lives childhood conflicts (relating to important figures in the past) with the analyst in the here and now. This can be negative (when feelings for a punitive parent are transferred onto the analyst) or positive. Transference interpretations are at the core of psychoanalytic treatment. The erotic transference is based on severe childhood dependence and hostility.

Counter-transference involves the patient coming to represent a figure of the analyst's past since the analyst cannot deal appropriately with what the patient relates because these are jar with the analyst's own unresolved issues. Such unresolved conflicts and problems in the analyst interfere with his ability to work satisfactorily with the client and it because of this that training analysts are required to deal with trainee analyst's blind spots and bring them to conscious awareness.

Resistance is the client's attempts to block the process of developing *insight* to his unconscious. Clues to resistance include long silences, acting out behaviour, demeaning the treatment, inappropriate challenging of the therapist, lateness, and not paying for sessions. Resistance interferes with treatment. This can include *secondary gain* (privileges from being ill), fear of reaching painful feelings/memories, and resistance to change. Symptoms may also be wrestling guilt or need for punishment and the client may cling on to these feelings in order to deal with some of his guilt. He dreads cure because this would end the analysis and would cause the loss of the relationship formed with the analyst.

Patients demonstrate a **negative therapeutic reaction** by not improving during treatment or even disimproving because of an unconscious sense of guilt. Freud (1923) indicated that such cases cannot endure any praise or appreciation, their symptoms representing a need for punishment or suffering and their way of dealing with a harsh super ego.

As Freud (1914) pointed out that the patient does not remember anything of what he has forgotten and repressed but instead may **act it out**: instead of talking about conflicts the patient enacts them (**acting in** therapy).

Triangle of conflict includes hidden feelings, defences against them, and anxiety lest defences do not work. (Grant, 2007, p. 110)

Working Through is required if lasting changes are to happen. Conflicts need to be worked through many times. Patients resist change and are compelled to repeat the past. Attempts to avoid change despite understanding must be dealt with repeatedly.

³³¹² Infants were born 'polymorphously perverse', i.e. a child may derive libidinal pleasure from various body parts.

³³¹³ 'Body damage anxiety' in boys and girls may be a more accurate reflection of what actually occurs. Freud was wrong when he believed that girls and boys focus only on the penis. In reality, girls focus on the genitalia as much as boys do on theirs.

*Psychoanalytic psychotherapy*³³¹⁴ recognises the development of transference and resistance and, depending on the number of foci, can be long-term or brief. Psychoanalytic psychotherapy is normally more focused, based more on the here-and-now, less determined to reconstruct developmental conflict origins, and more likely to use clarification, suggestion and learning through experience than psychoanalysis. There are three phases. The opening phase involves dealing with magical expectations and the desire for rapid symptom relief. Current problems, defences, coping styles and the developmental roots of the central issue are the subjects of examination. The middle phase is preoccupied by resistance and negative transference. The patient feels frustrated. Defences are analysed. Working with the transference is crucial. Termination and resistance to the ending of therapy occupy the end phase.

*Psychoanalytic group therapy*³³¹⁵: An individual member of the group may be treated whilst in the group (analysis within the group, associated with Wolf and Schwartz), the group transference may be the focus of interpretation (analysis of the group, associated with Bion and Ezriel), or there may be analysis through and of the group, the latter technique being associated with Foulkes.

*Brief*³³¹⁶ *dynamic psychotherapies*: Practitioners of brief dynamic therapy utilise ‘selective attention’ and ‘benign neglect’ in order to prevent being swamped by the client’s complex emotional experiences.

Treatment is supposed to initiate a process of change that continues long after termination of sessions.

Treatment may be needed on a number of occasions over the life span. The therapist is more verbal than in psychoanalysis. (Fleggenheimer, 1982) Clients are usually highly selected and highly functioning. Good ego strengths, rapid involvement in and contribution to therapy, a history of meaningful relationships, an adequate IQ and psychological sophistication indicate suitability for this type of intervention. Psychosis, major affective disorder, drug abuse, suicidal risk, impulsivity, organic brain disorder, and borderline or schizoid personality disorder indicate non-suitability. (Malan, 1963)

Gabbard et al. (2002) in their review of psychoanalysis and related therapies, reported that there was ‘preliminary evidence’ suggesting that ‘psychoanalysis’ is consistently helpful for people with mild disorders and is ‘somewhat helpful’ for those with severe conditions.

Bioenergetics: Wilhelm Reich formulated the view that body posture and movement can reveal attitudes and defences, so-called ‘character armour’. This idea led on to bioenergetics (Lowen, 1958) that aims to interpret these messages or meanings for the patient. Exercises (relaxation, breathing, massage, etc) are used to alter posture and behaviour and release muscular tension. The hope is that such changes will alter psychological function and self-expression.

Rogierian client-centred therapy consists of open and frank discussion of concerns. The Rogerian therapist shows ‘accurate empathy’, ‘non-possessive warmth’, and ‘genuineness’. The emphasis is on the positive qualities of clients. Negative feelings and deeper problems are ignored.

Transactional analysis (TA) is fairly superficial. It is usually conducted in a group format, but can be individual. It attempts to look at what part of the self – parent, adult or child – is used in communicating or ‘playing games’. Such communication may be inappropriate and maladaptive. The aim is to relate in a more appropriate and direct fashion (adult to adult) and learn mature problem-solving techniques.

Gestalt therapy³³¹⁷ holds that abnormal behaviour derives from aspects and feelings being split off, denied or repressed. The aim is to reconstitute wholeness or *Gestalt*. Gestalt therapy is usually conducted in a group. Direct communication is stressed, yet one can become angry at objects instead of people, e.g. break a chair or bash a pillow in order to get in touch with feelings.

Family therapy (Barker, 1986) involves all the members of a family. The family may act as a source of stress for the identified patient, it may be a resource for the patient, or it may serve to maintain the patient’s difficulties. (Harari & Bloch, 2008, p. 684) In the therapeutic community setting of Maxwell Jones the patients and staff meet regularly to govern their own affairs along democratic lines. The family is the most continuous source of care for and interest in the patient in the community. Crisis in the family should be dealt with by anticipatory action, the professional must be seen by the family as being of positive

³³¹⁴ Psychoanalytic-oriented therapy, psychodynamic psychotherapy, or explorative psychotherapy.

³³¹⁵ Initiated by Wolf and Schwartz.

³³¹⁶ Freud often practiced quite brief therapy, duration of treatment tending to lengthen after Freud. (Levenson et al., 2003) Ferenczi and Rank advocated time-limited therapy during the 1920s, and idea later taken up, among others, by Alexander, Malan, Sifneos and Davanloo. Catalysts for brevity include fiscal constraint (managed care in US), a need for more rapid relief than can be found in full analysis, and a need to reach a greater number of patients.

³³¹⁷ Introduced by Fritz Perls of the Esalen Institute in California.

assistance, and some member of the clinical team should be available to help the family for as long as is required.

Symptoms or disturbed behaviour of one family member is viewed as an expression of total family functioning. The cause is not to be found in the individual but must instead be understood in terms of the interaction and feedback between family members. Much of family therapy derives from systems theory, itself a daughter of *cybernetics* or the study of control, regulation and communication. Families communicate via instrumental (practical doing) and affective (feeling) channels. A child may get caught up in inter-parental problems (*triangulation*). Alliances within the family, such as mother-son v stepfather, may be abnormal and dysfunctional.

Family therapy terms

Collateral therapy – one therapist sees spouse/family subsystem and other therapist sees other spouse/family subsystem

Co-therapy – pair of therapists attend together at sessions

Conjoint therapy – therapist(s) meet spouses or parents and children together in same session

Family time line – chronology of events graphically displayed

Genogram – systematic family tree with life cycle and family history issues graphically displayed

Cultural genogram – a genogram that captures cultural; issues e.g. migration, immigration, and acculturation

Group therapy - therapist(s) meet with a number of couples/families in same session

Team participation – colleagues observe (as through a one-way screen) and give feedback, support, etc

Double bind – conflicting messages cause confusion, anxiety, and loss of sense of identity

Enmeshed family – non-permeable boundary with outside world; no interaction with extramural happenings; problems hidden within nuclear group, e.g. anorexia nervosa

Disengaged family – opposite to enmeshed; overt problems; ill-defined boundary with external world, e.g. delinquency

Semi-permeable boundary – this characterises most families; members feel like they belong to a family but are able to interact with the outside world

Boundaries – these are important between the outside world and the family but also between family subsystems, e.g. child v parents (too close or too distant, etc)

Hierarchy – a consistent healthy hierarchy is required within the family; this will be challenged by, e.g., adolescent rebelliousness

Family therapy approaches³³¹⁸ can be either problem-solving (brief, focused and pragmatic) or intergenerational (exploratory and growth oriented). Problem-solving approaches can be structural (associated with Minuchin), strategic/systemic (Palo Alto Group, Haley and Madanes, Milan [Palazolli, Boscolo, Prata, Cecchin] approach, etc), behavioural (Patterson, Alexander, etc) or psycho-educational (Anderson, Falloon, etc) whereas intergenerational approaches may be psychodynamic (Ackerman, Boszormenyi-Nagy, etc), Bowen-inspired (Bowen, Georgetown Group, etc), or experiential (Satir, Whitaker, etc).(see table) Narrative family therapy (White of Australia, Epston of New Zealand, and Tom Andersen of Tromso) is another approach. An integrationist approach (using interventions derived from different approaches) is gradually replacing strict adherence to individual ‘schools’.(Ritvo ea, 2008, p. 1317) Indications and contraindications for family therapy are summarised in the table.(Glick ea, 2000, p. 593-651)

Approaches to, indications for, and contraindications for family therapy

Approaches to family therapy summarised

Structural

- The problem indicates imbalance in family organisation, especially a malfunctioning hierarchical arrangement with unclear parent-child subsystem boundaries
- Symptoms often reflect maladaptive reaction to change/developmental requirements (e.g. life-cycle transition)

³³¹⁸ Classification systems vary.

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- Child-focused problems are symptoms of system in trouble and are used to detour inter-adult conflict
- Strategic/systemic*

- Focus on immediate social situation of identified patient
- Assumes all problems have multiple origins
- Presenting problem is a symptom plus a reaction to family dysfunction
- Learn family language and conceptualisations in order to see problem from family viewpoint
- Initiate change to help un-stick family from unworkable patterns that maintain symptoms

Behavioural

- Family rules/communication processes important
- Focus on interactional behaviours and conditions under which social behaviour is learned, influenced and changed
- Often used for marital conflict and with families containing behaviour disordered offspring
- Relationship failure results from deficient reward exchanges, as in coercive control
- Symptoms/maladaptive behaviour is reinforced/rewarded by family

Psycho-educational

- For families containing patient with serious mental illness, chronic physical disorders, or undergoing stressful lifecycle changes
- Provides education/concrete guidelines/support
- Views family as collaborator (not as a cause, as in schizophrenia)

Psychodynamic - Conceptualises family interactions in terms of

- Object relations - relation between subject and object as unconsciously perceived by the subject; internal representations of people that are not necessarily realistic
- Internalisations
- Introjects/projection – do the adult partners act in non-neurotic way – symptoms reflect attempt to work through conflictual material – may scapegoat member – look at behaviour of various generations for clues to current functioning – members must directly confront one another to resolve conflicts

Bowen approach

- Highly anxious and emotionally reactive relationships
- Stress can make matters worse
- Aim to resolve conflicts with families of origin

Experiential

- Life experiences cause the present problem
- Old pains propagated by current stress
- Resolve problems via open, intensive, affective, spontaneous interaction
- Employs sculpting and role play

Narrative

- Change occurs through new language
- Families are 'stuck' by 'stories' (possibility-limiting narratives) and constricted dialogue
- Need to uncover main stories (beliefs, culture) and bring more optimistic stories to the forefront
- Deconstruction (problems are not synonymous with people) and reconstruction (new ways of seeing stories) – the family joins together against identified (named) stories rather than against the member who has the problem
- Focus on times when person acted as if problem did not exist
- Reflecting team – clinicians watch via one-way mirror and then share observations
- Ideas are not right or wrong but are helpful or unhelpful
- Letters to patients after sessions constitute the clinical record

Brief solution focused

- How do family members relate to each other?
- Use findings to create novel strategies, e.g. people who do not express strongly felt feeling may be told to practice arguing

Indications and contraindications for family therapy summarised

Indications

- Family requests it
- Symptoms precipitated by relationship problems
- Child/adolescent is presenting case
- Changes in one member significantly affect another member
- A member reinforces symptoms in a co-member
- Sexual problem/dissatisfaction present
- Family disrupted by crisis/transition
- To investigate/influence severe mental disorder in one member

Contraindications

- Needs to be delayed until some other procedure is undertaken, e.g. detoxification from alcohol
- Family seems at ease with problem (ego syntonic)
- Family do not want external intervention (e.g. for religious/cultural reasons)
- Family are using the therapy to evade individual responsibility for personal problems
- Patient demands individual therapy only or patient needs help to individuate
- Failed family treatment where a member still needs help
- Family denial of problem or absence of crucial family members
- Aspects of one member (paranoid, manic, agitated, violent)
- Sufficiently significant parental pathology that indicates seeing child alone is the correct course to take

Marital therapy: It has been said that marriage is a great place for kids to grow up in but a poor place for the married couple to grow up in! A person's strongest interpersonal relationship, if positive and stable, acts as a buffer against any genetic tendencies to illness. (Ritvo ea, 2008, p. 1316) Marriage is about giving and receiving and about compromise. Many influences come to bear on a relationship, such as occupational stresses, sharing child-rearing decisions, growing old, and past and present issues relating to families of origin (breaking the umbilical cord, expectations derived from parents, looking after grandparents, etc). Whatever technique is employed³³¹⁹ (psychodynamic, behavioural or systems), the therapist avoids becoming over-identified with one partner (taking sides and keeping secrets are taboo). The focus is on the interaction between the two partners, i.e. the relationship rather than the individuals involved in it. Structural and strategic marital (or family) therapies are derived from systems theory. The term 'couple therapy' accommodates an 'unmarried but committed couple' (Fields ea, 2003, p. 1373) e.g. homosexuals.

Some approaches to marital therapy

Psychoanalytic/psychodynamic – unconscious processes originating in childhood but operating currently in the dyad and as transference reactions to the therapist; the therapist aims to reveal these to the conscious minds of the couple

Systemic – behaviour has a role, a meaning and a purpose in the system; areas of interest include use of language to manipulate the emotional space between couples and the use of power in the relationship; the therapist may seek parallels between what is happening now and how the couples' parents acted; problems may be reframed/redefined, e.g. a depressed husband may have assumed this emotional position to prevent his anger being directly expressed

Emotionally-focused – based on attachment theory; the therapist tries to more secure ways of experiencing emotion and to decrease the maladaptive responses (e.g. tension and avoidance) to perceived insecurity

CBT – up to 25 sessions; unwanted thoughts and behaviours are targeted; techniques include communication skills training and homework

Contraindications to marital/couple therapy

On-going violent/dangerous relationship

Violent partner does not/cannot commit to non-violent contract

Only one member wants to change or work on improving relationship

³³¹⁹ Modern approaches tend to be more integrative, here-and-now-based, and more likely to consider how the current problems arose over time. (Ritvo ea, 2008, p. 1322)

Active (extra-marital/couple) sexual liaison told to therapist 'in secret'
 Many attempts at therapy end in failure and current relationship is cold and untrusting

Interpersonal psychotherapy³³²⁰ (IPT): Interpersonal psychotherapy aims to reduce some of the social problems that may provoke or prolong an episode of depression, e.g. loss of a close relationship or interpersonal conflict. Such events need not have directly caused the depression but should have occurred around the same time as the lowering of mood. Specific targets (selected interpersonal focus areas) include abnormal grief, role transitions, role disputes, and interpersonal deficits. The therapist is active and supportive. Areas of enquiry include options and expectations in relationships. Role-playing is used in order to perfect tactical approaches to problems. There is no analysis of transference and no emphasis on homework. Toward the end of therapy, the therapist reinforces client competencies and the patient learns how to recognise triggers for depression. There is evidence that IPT improves social functioning but (unlike with CBT) personality disorder may adversely affect outcome in treating depression.(Joyce ea, 2007) It can be used as alternative or adjunctive treatment for depression. It has also been used in the treatment of bulimia nervosa. IPT performed better than CBT in a meta-analysis of studies of psychological interventions aimed at preventing onset of depressive disorders.(Cuijpers ea, 2008) Availability and training are problematic.(Markowitz, 2003, p. 1219) A maintenance form of IPT has also been developed in which long-standing patterns of maladaptive interpersonal behaviour become the focus of treatment.(Frank, 1991) Also, 'interpersonal counselling', an adaptation of IPT with a maximum of 6 sessions and often delivered by nurses, is designed for sub-syndromal patients in primary care settings.(Klerman ea, 1987)

Psychodynamic-interpersonal therapy³³²¹ (PIT): The main components are a rationale for exploratory treatment, development of a shared understanding, focus on the present, 'staying with feelings', understanding interpersonal issues, a sequence of interventions, testing solutions, and examining barriers to change. The one-sided relationship of traditional psychoanalysis is jettisoned for a negotiating style. Metaphors used by the client are used to help in understanding. PIT has been used to treat depression, anxiety, deliberate self-harm, and somatisation.(e.g. Guthrie ea, 2001)

Cognitive therapy/cognitive-behavioural therapy or CBT (see tables; Sudak, 2006; Gaudiano, 2008; Friedman ea, 2008): Beck ea (1979) hold that depression is maintained by misinterpretation and distortion in the evaluation of events³³²². This, they hold, is achieved through selective attention (remembering unpleasant events more than pleasant ones), arbitrary inference (attaching undue importance to minor events), and magnification (construing events in ways detrimental to the self when there is no basis for doing so). The notion of the 'cognitive triad' includes devaluation of self, a negative view of life experiences, and a pessimistic view of the future. The dysfunctional assumptions that need to be identified and challenged are not based on current reality, are rigid, over-generalised ('Absolutely everything I do goes wrong') and extreme, they block rather than further achievement of goals, they are associated with excessive emotion when thwarted, and are difficult to alter in the face of daily experience. Patients with such assumptions set excessively high standards for themselves, crave acceptance, and want to be strong. CBT has been applied to various problems, including depression, anxiety, personality disorders, eating disorders, and, with somatic therapies, psychoses. It is held that different psychiatric disorders are associated with distinct cognitive profiles (the *cognitive content specificity hypothesis*³³²³). The requirement of 'cognitive flexibility concerning delusions' may rule out many psychotic patients.(see Turkington ea, 2006) There is no evidence that negative cognitions are a cause rather than a consequence of depression and the presence of the expected cognitive set is not predictive of response to CBT.³³²⁴ Also, successful drug treatment in the absence of CBT provides remission of negative cognitions.

³³²⁰ This non-interpretative, non-cognitive, non-behavioural, here-and-now-focused therapy was developed by Gerald Klerman ea (1984) and is based on the work of Adolf Meyer, H S Sullivan, Frieda Fromm-Reichman and John Bowlby. Klerman, a psychiatrist, and Myrna Weissman, a psychologist, adapted the approach of social workers who focused on current interpersonal relationships.

³³²¹ This hybrid psychotherapy was developed by Hobson.(1985)

³³²² Beck's cognitive (or cognitive processing) model holds that affective response to an event depends on the meaning ascribed to the event.

³³²³ Anxious people feel threatened and vulnerable whereas depressive themes involve low self-esteem and loss.

³³²⁴ Burns and Spangler (2001) found no relationship between dysfunctional attitudes and treatment outcome in CBT-treated patients. Also, *acceptance and commitment therapy* (ACT) tries to reduce avoidance patterns without directly dealing with distorted cognitions.(Hayes ea, 2006)

CBT may be relatively ineffective in depressed adolescents.(March ea, 2004) Parker ea, (2003) who suggest that the efficacy of CBT in depression has been overstated, suggest seven possible ways in which it might work: modification of ongoing cognitive vulnerabilities (but they feel that it is the least cognitively impaired people who do best with CBT and that symptomatic improvement may predate cognitive restructuring), behavioural therapy component, non-specific therapy and therapist effects, a credibility effect, increased mastery over ones life, extended contact with a therapist, and acting on anxiety (or some other problem) for which depression is a downstream effect. The efficacy of CBT has been shown to differ between centres (Tarrier ea, 2004) and, based on a meta-analysis of ‘well-controlled trials’, Lynch ea (2010) found CBT to be no better than control interventions for schizophrenic symptoms or relapse rates, of small but positive effect for major depression, and not effective for preventing relapse of bipolar disorder. Among the various behavioural procedures employed in CBT are Socratic questioning (guided discovery), activity scheduling, graded task assignment, behavioural rehearsal, response prevention, distraction, relaxation exercises, breathing control, assertiveness training, modelling, and social skills training. Activity scheduling involves the use of a daily or weekly activity log wherein the patient records what was being done every hour of the day and rates each activity for mastery and pleasure. In graded task assignment a behavioural goal is broken down into smaller steps that can be taken one at a time. A typical course of CBT takes about 15 hours. CBT is not readily available in many areas (Department of Health, 1995; Taylor & Estroff, 2003, p. 606; Nutt ea, 2002, p. 88; Ballenger, 2004; Pollack ea 2004, p. 197; Stein, 2004, p. 7; Wilson & Shafran, 2005; Schatzberg ea, 2005, p. 341; Clark ea, 2009) and brief training courses may be ineffective.(King ea, 2002) CBT consists of many manualised interventions for numerous disorders, a fact that undermines training and application.(Olatunji ea, 2008, p. 199) Some patients require pharmacotherapy prior to CBT in order to make use of psychological interventions. Criticisms of CBT research include the use of comparator antidepressants in too low a dose for too short a period of time and the use of drugs in mild cases that might not be expected to respond.(Jarrett & Rush, 1994) CBT may be particularly useful for personality-disordered depressives³³²⁵. A perceived gulf between efficacy (in research) and effectiveness (in practice) of CBT among many experienced clinicians may be due to many factors, e.g. differences in clientele, training, workload, availability of CBT, or working outside specialist units (e.g. for eating disorders).(APA, 2002, p. 741) Luty ea (2007) found CBT superior to IPT for severe depression in outpatients. Publication bias (Cuijpers ea, 2010a) may have given an exaggerated view of the benefit of CBT for depression. We should make selective rather than blanket referrals for CBT.(Scott, 2008)

Cognitive therapy

Automatic thoughts³³²⁶ occupy a relatively superficial mental position. At a deeper level are schemas (less open to conscious awareness, deeper, reinforced by experience, core beliefs). Schemas are more difficult to identify and modify than automatic thoughts. Experience in recognising automatic thoughts should reveal underlying patterns/schemas. The patient should keep a list of uncovered schemas.

Techniques used for modifying automatic thoughts

- examination of evidence for and against
- decatastrophising – try to conceptualise feared outcomes in a way that promotes coping and problem solving
- daily record of dysfunctional thoughts – use columns – stressful events, automatic thoughts – score degree of own belief in such thoughts – emotional response – record more rational or realistic set of cognitions

³³²⁵ See Fournier.(2008)

³³²⁶ **Negative automatic thoughts** may refer to the self (‘I’m no good’), now (‘I can’t do anything correctly’), or the future (‘I will never improve’). These are due to processing errors leading to distortions, e.g. *overgeneralization* (sweeping judgements based on a single example, e.g. ‘Nothing I undertake succeeds’), *selective abstraction* (paying attention only to the negative, e.g. ‘It was doom and gloom all week’), *dichotomous reasoning* (extreme thinking, e.g. ‘If I don’t get every question right I’ll be a failure’), *personalisation* (accepting responsibility for things one has minimal/no control over, e.g. ‘I’m responsible for my boss’s mistakes’), and *arbitrary inference* (jumping to conclusions based on flimsy evidence, e.g. ‘I couldn’t handle the first assignment and therefore I’ll not be able to handle any other work I’m asked to do’).

- cognitive rehearsal – patient uses imagery or role play to identify possible distorted cognitions that could occur in a stressful situation and then work to modify them – the use imagery or role play again to practice the more adaptive pattern of thinking – then homework assignment wherein new cognitive patterns are tried out in vivo

Procedures used to uncover schemas

- Socratic questioning – guided discovery – help patient to move from a ‘closed mind’ to a state of inquiry and curiosity
- imagery
- role play
- thought recording

Interventions used to modify schemas

- examining the evidence
- listing advantages and disadvantages
- generating alternatives
- cognitive rehearsal

Options when treatment fails

- Continue treatment for longer
- For interpersonal issues consider a different approach, e.g. marital or family therapy
- Psychodynamic therapy or related approaches
- Somatic therapy +/- cognitive therapy

Selected research findings in CBT

1992. Relapse after CBT associated with slower response to therapy, single marital status, and high residual scores on Dysfunctional Attitudes Scale.

1999. In RCTs cognitive therapy (CT) more effective than drugs in 2/7 studies and equally effective in 5 others.

Specificity of CT/CBT questioned – when its components are removed it remains effective!

2002. Mild to moderate depressed outpatients given (a) TCA or phenelzine, (b) psychotherapy, or (c) ‘control conditions’: dropouts were 37.1%, 22.2%, and 54.4% respectively; ‘remissions’ were 46.4%, 46.3%, and 24.4% respectively.

2004. Four sessions of CBT given early to mildly/moderately injured A&E attenders modestly reduced symptoms of PTSD, but not depression or anxiety.

CBT is no better in schizophrenia than non-specific interventions.

2005. Combined CBT and mood stabilisers superior to mood stabilisers alone in terms of clinical outcome and cost-effectiveness for patients with frequently relapsing bipolar disorder.

2007. Cognitive self-therapy for depression or GAD decreases need for therapist input but was not proven superior to treatment as usual.

2008. Generic CBT for routine relapse prevention in patients recovering from a recent relapse of non-affective psychosis was unsuccessful.

RCT with children 7-17 years old with various anxiety disorders compared placebo drug, CBT, sertraline, and CBT plus sertraline: CBT and active drug reduced anxiety symptoms, combined treatment being superior to either treatment used alone; no child attempted suicide; and patients given CBT had less insomnia, fatigue, sedation, and restlessness than had children given sertraline.

Cognitive analytic therapy (CAT: Ryle³³²⁷ ea, 1992; Treasure & Ward, 1997): Heinz Hartmann (1894-1970) developed an ego psychology with the aim of replacing self-deception and misjudgements with new connections. As such his work exemplifies a partial bridge between psychoanalytic psychotherapy and CBT/CAT³³²⁸. CAT is time-limited (usually 16 sessions, sometimes more). The patient’s past and present is reformulated, the patient is assisted to recognise recurrent ways of formulating problems, and is help to revise such formulations. Negative assumptions act as ‘traps’ by causing a person to act in ways that cause consequences that reinforce those assumptions, e.g. excessive attempts at pleasing others³³²⁹. ‘Dilemmas’

³³²⁷ Dr Anthony Ryle was a GP who ended up as a consultant psychotherapist with the NHS in Britain. He was influenced by George Kelly’s (1905-1967) repertory grids (1950s) that present relationships in visual and mathematical formats.

³³²⁸ CAT focuses on relationship patterns whereas CBT focuses on symptoms, beliefs, and behaviour.

³³²⁹ The patient tries too hard to please in order to elicit care, is taken advantage off and feels angry, and then tries even harder to please.

are represented by false dichotomies: the often unconscious viewing of possible actions as black or white, with no shades of gray, e.g. the person who learned to hide their feelings from parents who ridiculed him now is caught between the loneliness of lack of emotional openness with others and the possibility of humiliation. More appropriate strategies are dismissed for consideration because of perceived 'snags': 'they wouldn't work because they are dangerous/forbidden/likely to meet opposition.' 'Sequential diagrammatic sequencing' is basically a diagram that helps the patient to remind him/herself of how he/she has used maladaptive coping strategies over time. The patient is helped to recognise automatic reactions in a timely matter, thus allowing time for consideration of alternative strategies. Other components of CAT include work done outside of therapy sessions (homework) and the exchange of (goodbye) letters that focus on what has been and what remains to be achieved.

CAT (Kerr & Ryle, 2006)

All mental activity is influenced by internalised experiences

This results in formation of 'a repertoire of *reciprocal roles*' (RRs: 'complexes of implicit relational memory, including perception and affect'³³³⁰

Most psychopathology stems from unhealthy RRs that manifest as 'self-perpetuating procedural enactments'

Latter may show as damaging relationships or poor self-care

Some enactments are feared or forbidden, as when self-assertion is disallowed by internalised 'voices' from parents or culture

Interpretations are not used in CAT because they are viewed as arising from theory and as attempts at convincing patients to accept what cannot be known to them. Patients who need further work may receive further sessions or psychoanalytic therapy.

Applications for CAT are developing, e.g. borderline personality disorder.

Cognitive behavioural analysis system of psychotherapy (CBASP: McCullough, 2006; Swan & Hull, 2007): This is a treatment for chronic depression developed by James McCullough of Virginia. Symptoms are believed to arise from arrested pre-operational³³³¹ (2-7 years) Piagetian development in early-onset cases. Late-onset cases are due to increased emotionality and regression. Interpersonal problems develop (and are perpetuated) from cognitive and behavioural patterns. Having learned this, the patient must now change maladaptive interpersonal behaviours. The therapist represents a stable interpersonal style. Kocsis et al (2009) found no significant benefit from CBASP as an augmentation strategy over flexible, individualised pharmacotherapy for chronic depression.

Dialectical behaviour therapy³³³²: This special form of CBT (Linehan, 1987, 1993) has been used in the treatment of borderline personality disorder. It consists of manualised weekly individual psychotherapy, group psychoeducation to improve skills, and, when indicated, telephone consultations. The aims are to teach problem solving (to help regulate emotions and tolerate distress), validation of perceptions, and meditation skills. Reflection prior to action is encouraged. Impulsive and self-destructive behaviour are not rewarded. It is hoped to include social effectiveness. A non-judgemental approach to events is encouraged. Linehan felt that conventional CBT mandated change and thereby reproduced the invalidating early experiences of the borderline patient. The DBT therapist shows that she understands why the patient acts as she does (i.e. their function) whilst acting as an advocate/guide for change. Missing a stated number of sessions leads to the patient not receiving DBT for a fixed period of time. (Sudak, 2006, p. 133) Dialectical behaviour therapy is probably more effective in reducing certain behaviours, such as self-harm, than in

³³³⁰ Early relationships with parental figures result in roles being gradually built into the mind (Cf. psychoanalytical *internalisation* and *schemas* in cognitive therapy).

³³³¹ Pre-operational functioning is represented by use of symbols, words and pictures to represent absent things; attending to part rather than the whole (centration); ability to accept what cannot be understood (intuitive thought); can only see things from own viewpoint (egocentrism); and inability to perceive conservation following change, e.g. in volume.

³³³² Developed by Marsha Linehan (University of Washington, Seattle), 'dialectical' refers to an attempt to help a person view **both sides** of an argument rather than focusing on one side only. According to Melanie Klein (1882-1960), objects, for the infant, are either good or bad, not both; part is confused with whole: breast is equated with mother and is either a good or bad breast depending on the service the infant receives. An ability to see that everyone has positive and negative attributes is a normal developmental acquisition

changing personality as such. (Linehan et al., 1993; Verheul et al., 2003) It has been described as ‘an elaborate and expensive treatment’ that is ‘demanding on those who would practice it’³³³³. (Palmer, 2002) Chiles and Strosahl (2005, p. 164) emphasise what clinicians have always known: ‘the repetitiously suicidal patient needs maintenance treatment that may span years if not decades’. The treatment team should have regular consultation meetings.

Rational emotive behaviour therapy (REBT): Developed by Albert Ellis, REBT assumes that thinking, emotions, and behaviour are interrelated. People may have poor tolerance for frustration and harbour illogical ideas (‘shoulds’). The aims of therapy are to alter beliefs and to allow behaviour to become more rational.

Coping skills training therapies: Coping strategies may be emotion- (anything that contains stress) and/or problem-focused (ways of managing events/difficulties) Therapeutic interventions include ‘stress inoculation therapy’ and ‘systematic rational restructuring’. The patient learns to use skills designed to help him cope with stressful situations.

Problem-solving therapies: The therapist teaches strategies that help others cope with problematic situations. Problems are identified, broken down into manageable components and skills (prioritising, brainstorming solutions, and making lists of advantages and disadvantages) to solve these are developed. These approaches have been shown to be effective in anxiety and depression in primary care and in helping people who self-harm. (Guthrie & Sensky, 2007, p. 801) Duration is 4-6 sessions, each of 20-30 minutes length. Only a short period of therapist training is required.

Mindfulness³³³⁴-based cognitive therapy: This approach (Segal et al., 2002), based on American work with patients experiencing chronic pain and somatic illness, is used to reduce the chances of relapse in recurrent depression. (Ma & Teasdale, 2004; Kingston et al., 2007) Patients are thought to disengage from their episodes of self-perpetuating ruminative, automatic thoughts so as to reduce reactions to them. Minds have a will of their own and what we do or feel may be determined by streams of thoughts about what belongs to the past or future. We should focus instead on the here-and-now. Unlike traditional CBT, the patient is asked not to engage with negative thoughts. The aim is to prevent minor drops in mood leading to depression via rumination. Usually conducted over eight sessions, the patient learns meditation (practiced regularly), breathing exercises, and yoga.

Behaviour therapy: This approach is based on learning theory: psychiatric disorders are seen as learned and therefore as being capable of unlearning. (see individual syndromes throughout text) There are 2 basic behavioural theories, Pavlovian (classical conditioning - the association of conditioned stimulus [CS] with unconditional stimulus [UCS] to produce the desired response – desensitisation³³³⁵ and implosion are probably best when there is a narrow range of anxiety manifestation with predominance of autonomic imbalance) and Skinnerian (operant conditioning - alternation of the frequency of a piece of spontaneous behaviour by means of reward, withholding reward or punishment). Punishment only produces short-term reductions in target behaviours when used alone and is more effective if combined with simultaneous reinforcement of desired behaviour.



Ivan Petrovich Pavlov (1849-1936) Nobel Prize 1904

Behavioural therapies useful for

Single phobias - desensitisation and flooding

Obsessional problems - response prevention, audiotaped habituation³³³⁶

Sexual dysfunction - Masters and Johnson techniques

³³³³ See also Hawton. (2005, pp. 205-6)

³³³⁴ The Buddhist notion (*Vipassana*) of *mindfulness* refers to non-judgemental awareness of personal experiences as they occur.

³³³⁵ *Self-control desensitisation* resembles ordinary desensitisation because it employs a hierarchical presentation of fear-relevant cues but differs from it by using various strategies to reduce anxiety during exposure, e.g. coping self-statements and cognitive challenges.

³³³⁶ Audiotaped habituation: used for obsessive ruminations – anxiety-producing thoughts are taped and played over and over again until there is significant reduction in anxiety.

Paraphilias - aversion, covert sensitisation – in the latter, the patient imagines target behaviour couples with something disgusting or painful
 Marital problems - contract therapy
 Enuresis - bell and pad
 Intellectual disability - behaviour modification
 Chronic schizophrenia

A phobia, for example, can be learned by classical conditioning, and because avoidance reduces the fear (hence rewards avoidance), it can be maintained by operant conditioning. This bringing together of both theories is known as the double learning theory. The more circumscribed the phobia the better the therapeutic results.

Behaviourists use directive treatment methods, with clear goals, and an objective measurement of outcome. Pavlov's experiments with dogs are well known. He paired food with a bell and the dog salivated.

Eventually the dog learned to salivate with the sound of the bell only. Operant conditioning employs immediate rewards following the appearance of the desired behaviour. The patient's speech or actions are shaped by the use of token economy³³³⁷. Token economy has become less popular because of fears that its effects might not last, that it deprived people of their rights, and that changes, if any, might be due to staff attention rather than the token. Operant techniques are probably best for behavioural problems in which there is some proportion of voluntary control.

The *Premack*³³³⁸ principle states that any frequently performed piece of behaviour can be used as a positive reinforcer of the desired behaviour. Intermittent reinforcement is more resistant to extinction than continuous reinforcement. *Shaping* involves providing successive approximations to the required behaviour, with contingent positive reinforcement. Behaviourists observe and concentrate on the symptoms or behaviour rather than, as in analytical approaches, looking for hidden psychic problems.

Desensitisation in imagination is not as effective as *in vivo*³³³⁹ desensitisation as the patient may fail when he faces a real feared situation. Safety seeking behaviours³³⁴⁰ that are practiced or even thought to be available diminish the outcome of exposure to the feared stimuli and patients must agree not to employ such behaviours; it is best to concentrate on the 'core threat' during exposure³³⁴¹. *Flooding* (implosion) is rarely used today compared with the past because of the extreme stress involved and the relatively equivocal results.

Behaviourist terminology

Avoidance training: one learns to remove oneself from the source of a noxious stimulus before it can happen, e.g. a bell forewarns a rodent of a forthcoming shock.

Chaining: piecemeal addition to a behavioural chain that eventually produces a full action. The first bit of behaviour is reinforced, the two bits, etc. For example, holding a spoon, then holding the spoon and putting it in the mouth, and so on, in an attempt to teach a child how to eat. 'Forward chaining' and 'backward chaining' are terms used when the first and last steps in a desired sequence are reinforced first respectively.

Classical: used to account for development of emotional responses – automatic, involuntary behaviour, such as reflex response to physical stimulus.

Classical conditioning (respondent learning): leads to unconditional reflex arising from a stimulus that does not normally produce it – this new stimulus is called a conditional stimulus, i.e. its ability to so is dependent upon/conditional on its having being associated with the unconditional stimulus.

Conditional reflex: reflex produced/elicited by the conditional stimulus.

Conditioning: a very simple form of learning.

³³³⁷ *Token economy* was employed extensively in rehabilitating chronic inpatients. A token (e.g. a coloured ticket, or, in practice, a cigarette) was given for desired behaviour (e.g. using an ashtray instead of the flowerpot to douse a cigarette). This token was added to those already collected. Tokens were used in exchange for privileges, such as a visit to the cinema or extra time in the TV room.

³³³⁸ David Premack (b. 1925, South Dakota) professor of psychology, University of Pennsylvania, did groundbreaking work on language and symbols in chimpanzees.

³³³⁹ The best results from exposure occur with real life exposure, longer exposure, and regularly practiced exposure with homework tasks. (Drummond & Warwick, 2007)

³³⁴⁰ E.g. the patient who fears elevators goes on one but brings a friend or a mobile 'phone with him.

³³⁴¹ E.g. the patient who fears heights leans against a balcony with hands clasped behind his back, i.e. he employs an 'opposite action' to that which he might ordinarily use (e.g. hugging a wall).

Continuous reinforcement: every occurrence of a particular behaviour is followed by reinforcement.

Discrimination of stimulus: learns to respond to one stimulus but not another.

Escape training: one learns to do something because it removes a noxious experience.

Extinction: loss of learned response due to absence of reinforcement

Generalisation of stimulus: after learning to smile at a parent the child proceeds to smile at others.

Incubation: reinforcement of avoidance due to brief exposure to feared object or situation.

Intermittent reinforcement: behaviour reinforced only some of the time – in general, intermittent reinforcement renders learned behaviour more resistant to extinction.

Modelling: a form of observational learning wherein one learns by watching someone carrying out an act. It is employed to treat phobias and as part of social skills training.

Negative reinforcement: behaviour occurs because of removal of a ‘reinforcer’.

Observational learning: process whereby one learns a response vicariously by observing an event and its consequences.

Operant: a desired piece of behaviour; used to account for development of voluntary behaviour, such as social, language and motor skills.

Operant conditioning (instrumental learning): concerned with behaviour that is under control of the individual, i.e. he ‘operates’ on the environment using it; how frequently he performs an operation depends on the consequences.

Positive reinforcement: behaviour increases because of addition of a ‘reinforcer’.

Paradoxical intention: reduce anxiety by encouraging subject to carry out feared action.

Prompting: learner is guided by verbal or physical prompts to make the required response.

Reinforcers: a stimulus or event that reinforces a given behaviour, e.g. escape for noxious stimulus, receipt of food, etc. Can be ‘primary’ (satisfies a basic drive, as food does for hunger) or ‘secondary’ (not occurring naturally –acquires this property by regular association with primary reinforcer, e.g. bell associated with food causes lever to be pressed in attempt to get food even when food is not forthcoming).

Reward training: one does something more frequently because of rewarding consequences.

Shaping: method of successive approximations - shaping reinforces behaviour that gradually becomes more similar to the final, required behaviour.

Spontaneous recovery: reappearance of apparently extinct behaviour.

Unconditional (unconditioned) reflex: natural, innate, occurring without previous learning.

Unconditional stimulus: stimulus that brings about an unconditional (unconditioned) reflex.

Simply removing a fear may not suffice, e.g. attention may need to be given to changed interpersonal relationships as a result of the behavioural intervention, e.g. a spouse may be left without the praise given for accompanying a husband/wife on the elevator – it might have been wiser to have involved her somehow in the treatment process.

Behavioural activation (BA): Developed by Neil Jacobson and others in the University of Washington, BA grew from an attempt to remove the ‘cognitive’ from CBT. The withdrawn, avoidant depressive is trying to avoid feared consequences of becoming involved. Depressive thinking *per se* is more important than what one is thinking. The patient is coaxed to become involved in pleasant, meaningful, and necessary activities. There is evidence of equivalence between BA and medication in preventing relapse of severe depression, and statistically significant superiority of both to cognitive therapy. (Temple & Geddes, 2008, p. 511)

Relaxation: Decreased oxygen consumption and a fall in blood pressure/heart rate/respiration rate accompany the ‘relaxation response’. Of importance for the relaxation response are quiet, decreased muscle tone, repetition of a sound, word or phrase (e.g. ‘relax’) silently or audibly, and a passive attitude. The response is mediated by the parasympathetic nervous system. The instructions given to the patient might include that he sit quietly in a comfortable position, close his eyes, deeply relax all his muscles (start at feet and progress to face, and then keep them relaxed), and breath through his nose (become aware of your breathing - during each expiration say ‘relax’, or whatever helps, silently to yourself). This should continue for 20 minutes. The patient may open his eyes to check the time but should not use an alarm. At the end, he should sit quietly for several minutes, at first with the eyes closed, then with opened eyes. He should not worry about how well he is doing and he must ignore distracting thoughts. The client should practice twice

daily (not within two hours of meals - digestion possibly interferes). The doctor/therapist should practice relaxing and exude confidence in the procedure.

Social skills training: This type of therapy/training has traditionally been carried out by occupational therapists. The aim is to assist individuals to relate to others with confidence and without undue anxiety and to cope with demands of daily living. The approach is primarily behavioural: role play, modelling, positive reinforcement and practical assignments. With the intellectually disabled or the chronic psychotic patient it is often necessary to commence with 'living skills' training, e.g. shopping, value of money, cooking, etc. One can then proceed to coping and interactional skills, e.g. how to conduct a conversation or to make a job application. A review of nine randomised controlled trials in schizophrenia found no significant reduction in relapse rates from social skills training regardless of length of follow-up, and a tendency for more dropouts than with the comparison treatment. (Pilling ea, 2002a) These results are described as 'disappointing'. (Bebbington ea, 2002)

Assertiveness training: Patients are trained to assert themselves, to say what they mean to say, to self-express in body language, to manage anger, to give compliments, and so on. Features include instruction, modelling and role-play.

Reminiscence therapy is an attempt to assist elderly and confused patients with memory problems to improve their social interaction. It is often conducted in weekly group format. Personal and historical past events are discussed. Audio-visual presentations, music, photographs, newspapers and other media may be usefully employed.

Art therapy can involve various media, varying from water colours to pottery. At its most basic level the emphasis is producing art without attempting to interpret it. The therapist may look for aspects of the therapeutic relationship or a reflection of the person's past in the artwork and tell the patient about this (art psychotherapy) or a deeper transference-related interpretation may be proffered (analytical art psychotherapy: Schaverien, 1991). Serial artwork may reflect changes in mental state, e.g. reality-orientation or affect. The hopes are that art will enable clients to express what they find difficult to verbalise and to facilitate psychological change. There are important concerns around inter-rater assessment reliability and the ability of raters are able to tell which works were done at the various stages of art therapy! (Eitel ea, 2008)

Music therapy involves making or listening to music with a trained music therapist. There is evidence that patients with a wide spectrum of serious mental disorders benefit from this modality, especially when the treatment is prolonged. (Gold ea, 2009)

Reality orientation is an attempt to maintain orientation in cognitively disturbed people. Large clocks and visual display boards (giving day, date, time, place, weather, next meal, etc) are employed. Staff must reinforce the information regularly. However, this approach needs to take account of the needs of each individual and practitioners should not confront their charges (Simard & Sampson, 2008, p. 237) if they are to avoid causing frustration, anger, and depression.

Cognitive remediation

Patients with schizophrenia have problems with attention, processing speed, memory, planning, and abstraction. Patients practice on laboratory-derived tests of cognitive function or on procedures designed to address cognitive deficits. Pilling ea (2002b) examined four randomised controlled trials and found very little support for cognitive remediation. Dickinson ea (2010) found that measured improvements failed to generalise, e.g. there was no improvement in function.

Hypnosis: Relaxation/alterd state of awareness is probably the basic therapeutic ingredient in hypnosis (Heap, 1988; Mathew, 1993; Kay & Tasman, 2006, p. 903 ff.). Alpha rhythm increases on the EEG during hypnosis. Studies involving attempts to block or reverse states of hypnotic analgesia with naloxone do not favour a role for endogenous opiates. (Maldonado & Spiegel, 2000) An alternative theory of hypnotic pain relief involves activation of descending antinociceptive mechanisms that exert control at the spinal level. Any condition or procedure, in which the patient is in pain, discomfort, or a state of tension, may be an appropriate indication. The patient may be hypnotised by a hypnotist and/or by self-hypnosis. Autohypnosis may help the patient feel in control of the process. Perhaps 10% (20-30% according to Maldonado & Spiegel, 2003, p. 1299) of adults are highly hypnotisable, 25% not being hypnotisable at all. There is no gender difference in hypnotisability. Hypnotisability is high for patients with PTSD, patients with pseudoseizures, and in those with severe dissociative disorders. It is said that patients with

schizophrenia, GAD, and, to a lesser degree, major affective disorder are difficult to hypnotise. The fact that a person is hypnotisable does not mean that hypnosis will be effective in that case. (Shader ea, 2003, p. 369) The *eye-roll sign for hypnotisability* (Spiegel & Spiegel, 1987) is a measurement of the distance between the lower border of the iris and the upper border of the lower eyelid (O, no change – 4, iris gone up behind upper lid and only sclera visible) when patient is instructed to gaze upward and lower eyelids. Hypnosis has had various applications, such as headaches (including migraine), bleeding (haemophilia), hypertension, asthma, the irritable bowel syndrome, stress-induced vomiting, drug-induced vomiting, duodenal ulcer (to reduce relapse rates), acute and chronic pain, dentistry, relaxation and anxiety control. Hypnosis aids recall of true and confabulated memories, and there may be a tendency to hold inaccurate memories with confidence following hypnosis. (Maldonado & Spiegel, 2003, p. 1319) Heap (1988) sees it as ‘an adjunct to therapy rather than a therapy in itself’. A number of authors deny that a state of hypnosis exists, (Wagstaff, 1981) whilst others worry about the potential for harm. (Hoencamp, 1990) Many authors are sceptical about patients’ ability to alter their immune system with hypnosis. (Covino & Frankel, 1999) The public often have exorbitant beliefs about the ability of hypnosis to ‘recover’ memories from the time of birth or even from past lives. (Maldonado & Spiegel, 2003, p. 1290) Patients should not be advised to start on a path of litigation or to confront others simply on the basis of ‘recovered’ memories. (Maldonado & Spiegel, 2003, p. 1321)

Motivational interviewing/motivational enhancement therapy has been mentioned in this text in relation to eating disorders, and alcohol and nicotine dependence. This empathic, non-judgmental approach attempts to win the patient’s active collaboration, to build a therapeutic alliance, to explore ambivalence (wavering), and examine the readiness of the client for change³³⁴². A cost-benefit analysis of change/no change is undertaken. Rather than dictating to the patient, he/she helps the patient to decide about change based on understanding/information. Common concerns, such as health status, are exploited. The *pre-contemplative* stage, where the patient has not yet considered change and may be under pressure from third parties (e.g. the boss or a spouse), is a time for empathic listening, information giving, and discussing the pros and cons for change. The *contemplative* stage is present when a client has done some thinking about the benefits and drawbacks associated with changing behaviour. Careful discussion aims at reappraisal of ambivalent thinking and bolstering of self-efficacy. The *determinative* stage simply infers that a decision to change has arrived. A course of action is discussed, as are ways of coping with the effects of change. During the *action* phase the patient must build up social skills, gather support, avoid precipitants (pubs, certain foods, etc), and continue to examine the negative consequences of reverting to former habits. Lastly, in the maintenance stage, relapse prevention strategies are employed (e.g. view transient drinking as a lapse rather a relapse to avoid catastrophising and giving up), to widen the repertoire of activities and skills, and to explore areas that might increase vulnerability to reversion to earlier maladaptive coping mechanisms.

Outcome research: Prioleau ea (1982) could find no convincing benefit over placebo for a ‘real patient’ of receiving psychotherapy and Storr (1979) and Wampold (1999) held that outcome is independent of underlying school of psychotherapy! Svartberg and Stiles (1991), in a meta-analysis of short-term psychodynamic psychotherapy, found greater changes in treated than in comparable untreated patients, but no difference in outcome for different forms of therapy. Outcome research has become more rigorous over the intervening years, (Roth & Fonagy, 1996) although Clare’s statement quoted at the start of this chapter is still held to be true by many clinicians. Knekt ea³³⁴³ (2008) compared short- and long-term psychodynamic therapies for mood and anxiety disorders and found that the former gave the quickest and the latter the best results, although they could not answer who would benefit from receiving either approach. Research should include an intention to treat analysis and also report on adverse effects such as excessive introversion, exacerbation of symptoms and acting-out behaviour. Dropouts from therapy should be followed up and reported. Compliance with somatic therapies has not been routinely monitored in comparative studies. Back in the 1950s, when psychoanalysis held sway, the typical characteristics of dropouts from therapy were described as poor, uneducated, non-integrated socially, less persevering with other treatments, and dissatisfied with treatment. Also, the stated form of psychotherapy in a published paper may not match what was given in reality. (Ablon & Jones, 2002) Controls are difficult to find for very long term therapies. (Levenson ea, 2003, p. 1171) Cuijpers ea (2010b) examined 115 RCTs of

³³⁴² The therapist points out discrepancies, ‘rolls with’ resistance, and contrasts the patient’s aims and behaviour.

³³⁴³ Helsinki Psychotherapy Study.

psychotherapy for adult depression and only 8 met the quality criteria³³⁴⁴ they had set; the resultant meta-analysis suggested that psychotherapy has significant effects but that the magnitude of such effects are much smaller than has been assumed.

Problems with randomised controlled trials and psychotherapy (Margison & Bateman, 2006)

Danger of randomising people to unsuitable treatment

Expectation of therapy influences outcome³³⁴⁵

Starts as random with small numbers and attrition thereafter (i.e. not random)

Different therapists employed who may differ in approach and adherence to protocols

Therapists rarely matched to patients³³⁴⁶

Non-specific factors influence outcome³³⁴⁷

Hard to achieve blind evaluations

Investigator allegiance influences results³³⁴⁸

Evidence-based research and psychotherapy (Bateman, 2007, p. 262)

Process-outcome research – informs on what works and how it works, maximising efficacy, improving treatment delivery

Measuring outcome – scale-derived scores (symptoms) are insufficient and batteries of measures inform more broadly on effects of therapy, e.g. change in social or interpersonal domains; must also look at avoided negative outcomes, e.g. suicide

Deciding on who measures outcome, e.g. patient satisfaction as part of the study

A *dismantling study* divides a psychotherapeutic package into component parts in order to test if the whole or part of that package is necessary to achieve the same outcome. For example, in a component analysis of cognitive-behavioural therapy, Borkovec et al (2002) compared applied relaxation plus self-control desensitisation, cognitive therapy, and their combination in patients with generalised anxiety disorder and found no significant differences between them.

A potential fallacy is that treatments, including psychotherapy, administered over long periods of time may coincide with a remission or resolution rather than directly result in cure.

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³³⁴⁴ The criteria were 2 independent coders, meeting diagnostic criteria for depressive disorder, treatment manual, trained therapists, check on treatment integrity, intention to treat analysis, more than 50 cases, independent randomisation, and blind outcome assessors.

³³⁴⁵ The common use of a waiting list comparison group is an inadequate method of studying psychotherapy. (Rifkin, 2007)

³³⁴⁶ Fonagy and Paris (2008, p. 110) suggest that the evidence for common factors in psychotherapy is so strong that we should examine how alliances are built rather than techniques.

³³⁴⁷ According to Orlinsky et al (2004) the most helpful factors in all psychotherapies are well-defined contract, strong alliance, encouragement of openness in the patient, and staying focused on current life problems/relationships.

³³⁴⁸ Luborsky et al (1999) suggest that researcher allegiance accounts for 70% of outcome variance.

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25

Psychotherapy with Children

26

Physical therapies

Brian O'Shea

*Electroconvulsive therapy (ECT)*³³⁴⁹

'It should not be relegated to a treatment of last resort'.(Lamprech ea, 2005)

There is no doubt that ECT was overused in the years immediately after it was discovered, so creating an unfortunate legacy that militates against its proper use today.



Outdated ECT machine

Availability, acceptability and standards

Strenuous efforts have been made to maintain standards in the practice of ECT.(Pippard & Ellam, 1981; Latey & Fahy, 1986; Andrade ea, 1993; RCPsych' Special Committee on ECT, 1994; Fergusson ea, 2003; Fergusson ea, 2004)

1992: European Court of Human Rights ruled in *Herczegflavy v Austria* that ECT did not amount to torture (Lepping, 2003)

Main goal for the future is to discover what central effect(s) of ECT are fundamental for efficacy (Fink, 2002)

³³⁴⁹ See also O'Shea.(2007a,b) In 1937 Cerletti and Bini (published 1938) induced fits by passing an electric current (ECT) between two electrodes placed on the front of the head. Ugo Cerletti was professor psychiatry in Rome from 1935 and Bini was his assistant. After preliminary work in Rome's slaughterhouses, where electricity was already in use to stun or kill animals, their first human subject was a schizophrenic patient who appears to have benefited. Bini realised that the high mortality among dogs given electrical treatment was the fact that placement of electrodes at head and rectum led to passage of current through the heart.(Abrams, 1988) No aspect of electricity is essential to the benefit of ECT.(Fink, 2002) Indoklon (ether flurothyl) inhalation, reported first in 1958, is just as effective as ECT but is not as 'clean' a procedure (could not be combined with a muscle relaxant and often caused a second fit). Photically induced convulsions (given without anaesthetic) are possible but are not employed in practice. The psychiatrist Abram E Bennett (1898-1985) of Omaha, Nebraska was the first to use a muscle relaxant with ECT, a curare preparation, in 1940. Holmberg and Thesleff of Karolinska Institute, Stockholm, suggested using succinylcholine in 1952. Unilateral ECT was introduced by E Friedman and P H Wilcox in 1942 and was first used to minimise memory problems by J Thenon in 1956. About 20,000 people receive ECT annually in Britain.(Wise, 1997) In fact the numbers of individual ECT administrations fell in the UK NHS from 137,940 in 1985 to an estimated 65,930 in 1999.(Eranti & McLoughlin, 2003) It continued to fall in England to 2006 but the detained patients were more likely to receive it than in the past.(Bickerton, ea, 2009) The annual rate of ECT for Scotland was reported by Fergusson ea (2003) to be 142 individual treatments/100,000 of the total population. Use of ECT in the Republic of Ireland was officially reported for the first time in 2003: 859 people received this mode of treatment, although use varied by region from 38.7/100,000 in the South Eastern Health Board to 8.4/100,000 in the Southern Health Board.(Daly ea, 2004) In 24 approved centres in the Republic of Ireland in 2008 there were 407 'programmes' of ECT (9.6 programmes/100,000 population) with a national average of 6.7 treatments/programme.

Need for improvement in some procedural aspects, e.g.

Must have a designated ECT consultant in centre carrying out ECT or an ECT team (with designated members) serving a number of centres

Use of recommended machines, regular servicing of machines (Andrade *et al*, 1993)

Better supervision of junior medical personnel³³⁵⁰

Training in explaining ECT to patients (Wise, 1997; Duffett & Lelliott, 1998; Trezise, 1998; Blaj *et al*, 2007)

Unmodified ECT is still used in Malawi, apparently without serious complications³³⁵¹ (Selis *et al*, 2008)

2008: *Mental Health Act 2007* (England & Wales): ECT cannot be given to a person who has capacity unless in an emergency, i.e. to save the person's life or to prevent serious deterioration in his/her condition; a 'Second Opinion Doctor' has to examine the patient; parental permission does not override the decision of patients aged 16-17 who have capacity

2010: ECT practice in Asia is suboptimal: schizophrenia is the main indication; sine wave is used; unmodified ECT is common; always bilateral; EEG use is uncommon; continuation ECT is rare; and there is no formal training (Chanpattana *et al*, 2010), although (recent) progress is being made in Japan (Takebayashi, 2010)

ECT is still used in the USA³³⁵², especially in private facilities.(see Hermann *et al*, 1995; Kramer, 1999), despite restrictive regulations and limited availability.(Weiner *et al*, 2001, p. 98) Prudic *et al* (2001) were not impressed with ECT standards³³⁵³ in a minority of New York facilities. Benbow (1991) found that most old age psychiatrists would consider using ECT in appropriate circumstances, especially for psychotic depression; most used bilateral ECT; and psychiatrists did not consider age to be a contraindication to giving ECT. Bhat (2003) predicted an increased use for ECT in elderly depressives. Although the literature consists mainly of single case reports (Rey & Walter, 1997), ECT in people under 18 years old has similar effectiveness and side effects as in adults.(Duffett *et al*, 1999a) ECT may be under used in the intellectually disabled.(Waarde *et al*, 2001)

Attitudes

Medical students

Have poor knowledge of ECT (Abbas *et al*, 2007)

Often very negative about ECT (Gazdag *et al*, 2005)

Knowledge and attitudes intermediate between MRCPsych trainees and lay public (McFarquhar & Thompson, 2008)

More positive after seeing patients receive it (Ryley & Friedman, 1991)

More positive after seeing patients receive it than simply receiving didactic instruction (Shah & Averill, 2009)

More positive after seeing patients receive it (Kinnair *et al*, 2010)

Australian mental health nurses

Rated ECT as a treatment for depression between that of psychiatrists and lay people – they preferred medication, counselling and physical activity.(Caldwell & Jorm, 2000)

Dublin nurses, including psychiatric nurses

Poor knowledge of ECT and negative attitudes to the procedure

Exposure to ECT did not change attitudes among nursing students (Byrne *et al*, 2006)

London mental health nurses

Exposure to ECT led to positive attitudes (Wood *et al*, 2007)

Turkish psychiatric nurses

Education about ECT improved nursing practice and increased patient satisfaction (Arkan & Üstün, 2008)

³³⁵⁰ An 'ECT training head' (Dantec Electronics in UK, distributors for Thymatron machine) is a dummy that offers experience in giving ECT and interpreting the EEG. According to Halliday and Johnson (1995) one in five doctors were not supervised when administering ECT for the first time in New South Wales.

³³⁵¹ No oxygen, anaesthetic or muscle relaxant is used. An English ECT device manufactured during the 1960s is in use (constant current, brief pulse waveform) although 2 newer machines have been donated from Scotland.

³³⁵² ECT was originally in favour in state institutions as a treatment of chronic illnesses such as schizophrenia.(Marangell *et al*, 2003, p. 1123) Less than 8% of all US psychiatrists provided ECT in 1998.(Hermann *et al*, 1998) Worries have been expressed that use of ECT in the US may be in decline despite its strong evidence base.(Levy, 2007) Hungarian psychiatrists, especially those dealing with outpatients, may have negative attitudes toward ECT, although their knowledge of the treatment was found wanting by Gazdag *et al*.(2004) ECT rates have increased in Australia where it is more likely, as in many countries to be given to older people.(O'Connor, 2008, p. 201) New Zealand psychiatrists are generally well disposed to ECT although they may resort to it somewhat less regularly than do British psychiatrists.(Strachan, 2001) Public use of ECT in Hong Kong is much less frequent than in the UK and a few private practitioners were noted to be using outdated technology.(Chung *et al*, 2003)

³³⁵³ Same electrical charge given to everyone, use of old sine wave stimulation, no monitoring of seizure duration, and failure to examine cognitive state.

Non-psychiatrist Indian doctors

More positive attitudes towards ECT if they had experienced practical work in psychiatry (Chakrabarti ea, 2003) although Chanpattana ea (2005) reported that about 50% of ECT was unmodified

Media

Unhelpful (O'Shea & McGennis, 1983; Andrade & Rao, 1996; McDonald & Walter, 2001; O'Shea, 2002; Dowman ea, 2005; McFarquhar & Thompson, 2008; Euba & Crugel, 2009)

Patients

Most patients reported that ECT helped them; that ECT had been adequately explained; and side effects were mild or moderate (Benbow & Crentsil, 2004)

69% of Australians who had ECT as adolescents would have it again if needed and 77% would recommend it to others; 92% rated depression and medication as worse than ECT (Walter ea, 1999)

'A Practicing Psychiatrist' (1965) was positive about the effectiveness of ECT and philosophical about side-effects.

Donahue (2000) received unilateral ECT (changed to bilateral), believed it saved her from suicide, could not remember parts of her life, and would have it again if needed.

*Relatives*³³⁵⁴

Turkish relatives of bipolar patients had positive attitudes toward ECT (Viritt ea, 2007)

'Guidance' from the UK National Institute for Clinical Excellence (NICE)³³⁵⁵ published in 2003 attempts to restrict the use of ECT to the level of a brief intervention³³⁵⁶ in severe depression, mania or catatonia.³³⁵⁷

Irish MHC (2008) definition of ECT

Medical procedure

Current passed briefly through brain via scalp electrodes to induce generalised seizure

A programme (course) of ECT consists of no more than 12 treatments (applications)

Irish MHC (2006) rules governing use of ECT, e.g.

Written consent required for ECT session including anaesthesia

Second consultant authorisation is needed for patients unable/unwilling to consent

Alternative therapies must be discussed with the client

The initial electrical dose must be determined in advance

Cognitive function must be regularly assessed

Anaesthetist must conduct pre-anaesthetic assessment

Designated ECT nurse carries out various duties e.g. checking that assessments are completed

Irish MHC (2009a, c) rules governing use of ECT, e.g.

Capacity to consent includes understands and believes broad consequences of not receiving ECT

Patient must be told about likely adverse effects, including cognitive impairment/amnesia

Initial stimulus dose must be discussed and agreed between treating and ECT-administering consultants

Perform cognitive assessment before and after each course ('programme') of ECT – keep copies in patient's file

Unless it cannot be so, use same ECT machine for each application

Monitor EEG with 2 channels

At least 2 registered nurses must be present in ECT suite

Irish MHC (2008, 2009b) code of practice for ECT prescribed for voluntary patients³³⁵⁸

³³⁵⁴ For a positive, personal view see Webber.(2009)

³³⁵⁵ NICE: www.nice.org.uk.

³³⁵⁶ Maintenance treatment excluded.

³³⁵⁷ This was welcomed by the mental health charity MIND and by Carney and Geddes,(2003) the latter having been involved in Department of Health systematic review work on ECT, but is seen as too restrictive by most British psychiatrists. Interestingly, NICE was advised by the WHO to 'break its close links with the drug industry and to make its processes more transparent'.(Kmietowicz, 2003)

³³⁵⁸ A *private* proposal by Irish senators that the *MENTAL HEALTH (INVOLUNTARY PROCEDURES) (AMENDMENT) BILL 2008* amend Sections 58 and 59 of the Mental Health Act 2001 as follows has been suggested by some:

1.—That Section 58 (psychosurgery) of the Mental Health Act 2001 be deleted.

2.—That Section 59 (ECT) of the Mental Health Act 2001 be deleted and replaced as follows—

(1) A programme of electro-convulsive therapy (ECT) shall not be administered to a patient unless the patient gives his or her informed

consent in writing to the administration of the programme of therapy;

(2) The Commission shall make rules providing for the use of ECT and a programme of ECT shall not be administered to a patient except in accordance with such rules.

A named consultant psychiatrist³³⁵⁹ should have overall responsibility for ECT
 Must have patient's³³⁶⁰ written consent to ECT/anaesthesia
 Consultant psychiatrist should be satisfied patient has capacity to consent³³⁶¹
 Patient must know that consent can be withdrawn at any time
 Coercion and threats should not be used
 ECT consent form must contain at minimum the particulars included in form suggested by MHC
 A registered medical practitioner working under responsible consultant's supervision must obtain written consent prior to each application of ECT
 Information must be oral and written, clear and simple, and interpretation/sign language made available as needed
 Unless an emergency is at hand, at least 24 hours to allowed for consideration of response by the patient
 If he/she so wishes; advocacy should be granted; and questions should be answers
 Only the responsible consultant prescribes ECT and he/she records reasons for prescribing, alternatives considered, initial stimulus dose, details of discussion, and current mental status of patient
 Clinical status is assessed before and after each application of ECT
 Reason for terminating a course of ECT is to be documented
 A consultant/supervised anaesthetist should give the anaesthetic and formally have the (correct) patient identified (see original document for details of other requirements)
 Designated ECT nurse checks equipment
 Constant current, brief pulse ECT machine delivering 25 to 1,000 milli-coulombs or more
 For details of ECT suite see original document

ECT is rarely used before 16 years of age.(Parmar, 1993) It can, however, be effective in prepubertal children, e.g. for mania.(Hill ea, 1997; Willoughby ea, 1997)

Patient preparation

Patients generally forget explanations about ECT and many fear it.(O'Shea & McGennis, 1983)
 Explanations need to be repeated as required throughout a course of ECT. Some degree of apprehension is normal and does not contraindicate ECT. The patient should be told that it is usual to have a memory blank for the time surrounding a course of ECT. A printed pamphlet or booklet can be of great help to patients and relatives. A signed consent form is essential,³³⁶² perhaps repeated every 6 months for maintenance ECT. People will differ later on how valid the consent given at the time was. This has been interpreted as either placing trust in the doctor or as reflecting inadequate attempts to get true consent.(Rose ea, 2005)
 Psychiatrists may be less likely to agree among themselves when it comes to giving ECT to seemingly incapacitated (lacking capacity) but compliant patients than when giving the same treatment to capacitated and non-compliant cases.(Law-Min & Stephens, 2006) The patient should receive an adequate explanation of the procedure and the reasons why it is being prescribed, the likely consequences of the treatment, and the consequences of not receiving ECT. He may need time to think about it or to discuss it with relatives or GP. In the case of patients who are unable to sign, because of their mental (including cognitive) status or legal status the local legal requirements should be followed. The (Irish) Mental Health Act 2001 requires

A major omission in the Mental Health Act 2001 is the lack of provision for treating voluntary patients who suffer deterioration of mental status but do not seek to leave hospital.(Dunne ea, 2009) The Wards of Court system is, in the author's experience, likely to take too long to take effect and may only become involved where there is a substantial estate.

3.—This Act may be cited as the *Mental Health (Involuntary Procedures) (Amendment) Act 2008*.

³³⁵⁹ Not necessarily the patient's responsible consultant.

³³⁶⁰ Consent must be given for each ECT programme (including anaesthesia) and for each individual ECT (including anaesthesia). Specific consent must be given for *maintenance/continuation ECT* and renewed after 6 months. The patient must be made aware that if ECT is refused alternative treatment will be offered. **No one can give proxy consent for ECT.**

³³⁶¹ I.e. can understand what ECT is, why it is proposed, understand risks/benefits/alternatives and broad consequences of not receiving ECT, retain the information for long enough to make decision, and be able to communicate decision. Likely effects of ECT including 'risk of short-term cognitive impairment' must be explained. Also, it must be confirmed that alternatives treatments will be given if consent to ECT is not given. Written record of capacity assessment kept in clinical file.

³³⁶² Or a witnessed mark, or documented and witnessed statement that a patient indicates non-verbally his/her consent non-verbally. Consent is sought for a course of ECT, not just for one application. Consent can be withdrawn at any time. Rush ea (2008) reported on 89 consecutive patient who received ECT in a private Dublin hospital: an average of 17 weeks post-ECT there were low rates of perceived coercion, high rates of satisfaction with consent procedures and information and staff support.

written consent from the patient and the agreement of two consultant psychiatrists, one being the treating consultant.

Normal precautions for a general anaesthetic are taken.

ECT is safer than tricyclic antidepressants (TCAs) in patients with severe cardiovascular disease. (Zielinski *et al*, 1993) Modern ECT procedures significantly reduce the risk of adverse cardiac outcomes. (Rice *et al*, 1994)

Certain items should be checked off as part of a pre-ECT nursing check³³⁶³ and the completed record kept in the patient's notes.³³⁶⁴

Outpatients

Have a relative at the centre or one arranged for journey home

Should not drive, operate dangerous machinery, or otherwise take risks

The digit used for pulse oximetry should be free of nail polish. Medication³³⁶⁵ may be required to reduce the chances of inhalation in cases of oesophageal reflux. There should be a sheet on which the anaesthetist notes details of the drugs given and other procedures carried out, and the psychiatrist notes the effects of the ECT and the dose (millicoulombs) used. Two-thirds of the population have a seizure threshold of 100-200 mC, but the range is probably 20-800 or so. Scott (2005, p. 141) suggests that the initial dose be 50-100% and 300-500% above seizure threshold for bilateral and unilateral ECT respectively. Fochtmann *et al* (2003) suggest that optimum benefit with unilateral ECT requires stimulation that is 'at least' 5 to 6 times the threshold. Recovery from the treatment should also be noted regularly, as should response of the underlying disorder and cognitive status.

Fochtmann *et al* (2003) suggest giving beta-adrenergic receptor antagonists to minimise the risk of thyroid storm in patients with significant hyperthyroidism who are going to receive ECT; also, patients with myasthenia gravis or upper motor neurone disease should receive a reduced dose of succinylcholine³³⁶⁶.

Indications and contraindications

Patients who have responded to ECT in the past may seek ECT again should they suffer a relapse. Andrade and Kurinji (2002) reviewed the literature on continuation (direct continuation of ECT over a 6 month period following a course of ECT) and maintenance (6 months or more after a course of ECT) ECT and declared it safe and effective for relapse- and relapse/recurrence-prone patients who have responded to a course of ECT. (Frederikse *et al*, 2006; see Fink, 2007; Gupta *et al*, 2008) Continuation and maintenance ECT may be useful for otherwise refractory unipolar depressives³³⁶⁷, bipolar patients, and depressed schizoaffectives. (Russell *et al*, 2003; Vaidya *et al*, 2003) Unfortunately, patients who are unresponsive to antidepressant drugs may experience less benefit from ECT than drug-responsive subjects³³⁶⁸. (Prudic *et al*, 1996) ECT is indicated primarily for depression, especially if psychotic depression (especially with retardation and delusions – up to 90% of psychotic depressives respond). Buchan *et al*³³⁶⁹ (1992) found that deluded-retarded cases lost twice as many points on the Hamilton Depression Scale as did a group without these characteristics. However, Sobin *et al* (1996) concluded that ECT is a viable option for major depression regardless of the presence of psychosis, retardation or agitation. ECT works quickly, although its effect may not last more than an average of one month. According to Prudic *et al* (1993), the degree of residual symptomatology shortly after ECT is not different between cases of dysthymia plus major depression and

³³⁶³ Completed for each application.

³³⁶⁴ Name, age, unit, whether consent form signed, and date, psychological preparation, anaesthetic consent signed, ECT actually prescribed this time, patient fasting for 6 hours (2 hours for clear fluids; check with anaesthetist if in doubt), bladder empty (supervised – rupture is a rare risk, mainly in elderly, patients on TCAs, and prostatic obstruction), rings (on fingers) insulated (with tape), dentures removed (rare possibility of inhalation), metal objects removed (including hair pins), cosmetic removed (hair should be clean and free of cosmetics – latter can lead to singeing of hair and interfere with induction of seizure), shoes and stockings removed, personal hygiene, garments loosened, valuables safe, case notes to hand, treatment card to hand, temperature, pulse, BP, urine tested.

³³⁶⁵ E.g. ranitidine, metoclopramide, or sodium citrate.

³³⁶⁶ **Cholinesterase inhibitors prolong the effects of succinylcholine.**

³³⁶⁷ Kellner *et al* (2006) found that continuation ECT and lithium plus nortriptyline were better than placebo in preventing depressive relapse but that half the patients relapsed or dropped out of the study.

³³⁶⁸ Patients who are unresponsive to antidepressant medication should either have a change of antidepressant or augmentation with, say, lithium.

³³⁶⁹ This study combined results from the Leicester and Northwick Park trials.

major depression only. Patients with major depression plus personality disorder may respond less completely (more residual psychopathology) to ECT and relapse more readily after ECT than patients with uncomplicated major depression.(Lee & Coccaro, 2002; Feske ea, 2004)

Higher electrical dosage above seizure threshold results in more rapid response in major depression, and probably also in schizophrenia.(Sackeim, 2003, p. 536) However, it also causes more cognitive problems. ECT may still has a few important applications in schizophrenia,³³⁷⁰ catatonia,³³⁷¹ mania³³⁷² (de Macedo-Soares ea, 2005) and indeed any psychotic state where an early response is essential, when there is a danger of suicide, where there is much suffering, or when drugs are contraindicated as in the occasional case of extreme hypersensitivity, unacceptable side effects or non-responsiveness.(Duffett ea, 1999b) Combination of antipsychotic drug plus ECT may be more effective than either treatment given alone.(Sackeim, 2003; Painuly & Chakrabarti, 2006) ECT can be useful in epileptic patients who become disturbed but without developing a convulsion (often only one application is required). It may reduce the frequency of petit mal attacks and terminate *epilepsia partialis continua*. ECT appears to be safe when combined with anticonvulsant drugs, although the literature is composed mainly of case reports.(Sienaert & Peuskens, 2007) Dementia *per se* is not a contraindication to ECT although confusion after ECT can be severe and prolonged. White matter hyperintensities (and evidence of basal ganglia disorder) on MRI has been blamed for post-ECT delirium (Figiel ea, 1990), although Coffey ea (1989) achieved excellent results with ECT in older people despite the presence of such hyperintensities.(see also Coffey, 1996) Down's syndrome patients can be given ECT.

Negroes - may need screening for sickle cells (sickling crisis may be precipitated by hypoxia during anaesthesia)

High myopes - at risk of retinal detachment; ophthalmological opinion may be needed

Eye surgery – use ECT with caution during the first weeks; time is needed for wound healing; if ECT is used it is suggested that non-depolarising muscle relaxants are used, that adequate oxygen is given to decrease cerebral vasodilatation, and that the patient is hyperventilated to diminish hypercarbia; gross visual acuity and field-testing should be carried out after the first treatment (Saad ea, 2000)

*Open-angle glaucoma*³³⁷³ - ECT, although causing a transient rise in intraocular pressure, has not been reported to cause problems

Closed- (narrow-) angle glaucoma - although extremely unlikely to be referred for ECT, cases pose a much more serious proposition; expert advice should be sought;

Prescribed anti-glaucoma medications - in general these should be given before ECT (Fochtmann ea, 2003, p. 381)

Reserpine - contraindicates ECT (both treatments cause marked vagal stimulation with possibility of cardiac arrest: Bross, 1957)

Asymptomatic/stable coronary artery disease – do not stop long-term cardiac medications on morning of ECT because this will increase risk for myocardial ischaemia (Tess & Smetana, 2009)

Cerebrovascular accident – normally wait a minimum of 1-3 months³³⁷⁴ before considering ECT; poststroke depression may respond to ECT (Weiner ea, 2001, p. 13)

Anticoagulants – maintain INR of up to 3.5 unless there is an increased risk of intracranial bleeding (e.g. tumour or aneurysm: Tess & Smetana, 2009)

Brain tumour - ECT may be given if CSF pressure is normal, there is no surrounding oedema on CT, there are no indications of an organic brain syndrome, and neurological examination is normal; various manoeuvres (e.g. steroids, antihypertensives, and hyperventilation) may be used to minimise rises in intracranial pressure

³³⁷⁰ Especially acute onset, short episode duration (as distinct from illness duration), bewildered, or disturbed mood.(Sackeim, 2003) Fear (2005) suggests trying clozapine first. See Chanpattana and Andrade (2006) for a discussion of ECT for treatment-resistant schizophrenia and their response to the UK NICE report.

³³⁷¹ From almost any cause, although benzodiazepines are first choice for the less severe case. Fear (2005) suggests ECT as first-line treatment for malignant catatonia.

³³⁷² Especially mixed mania-depression and severe mania. Clozapine plus ECT may be the ultimate treatment for highly refractory mania.

³³⁷³ Anticholinesterases with long duration of action may prolong apnoea from succinylcholine and should be replaced by alternative drugs for a period before giving ECT.(Weiner ea, 2001, p.41)

³³⁷⁴ Depending on literature source and stroke severity. Every case requires an individual risk-benefit assessment.

Asthma or COPD – taper and stop theophylline; continue other medication; for exacerbations before ECT give inhaled beta-agonists and, if needed, corticosteroids (Tess & Smetana, 2009)

Chronic steroid patients – although often given extra ‘stress doses’ before general anaesthesia evidence from 27 patients (Rasmussen ea, 2008a) suggest that this is not necessary before ECT treatments, i.e. simply give the usual morning dose before ECT

ECT may improve *Parkinsonism* or associated depression, or both³³⁷⁵

The serum prolactin declines as ECT proceeds: it rises with each ECT but the rise is blunted with subsequent ECTs.

Relative contraindications³³⁷⁶ to ECT

Raised intracranial pressure

Aneurysms in awkward places or of large size (repair first if possible, but many cases have proved durable, e.g. Mueller ea, 2009; short-acting IV medications³³⁷⁷ may be used to control BP: Drop & Welch, 1989; Tess & Smetana, 2009)

Active chest infection

Recent myocardial infarction³³⁷⁸ or CVA³³⁷⁹

Non-demand pacemaker³³⁸⁰

Uncontrolled hypertension³³⁸¹

Untreated pheochromocytoma

Critical aortic stenosis³³⁸²

Unstable fracture

Odontoid process erosion (rheumatoid)

Threatened retinal detachment³³⁸³

Some authorities inhibit the defibrillator function of an implanted cardiac defibrillator during each ECT treatment³³⁸⁴ and some clinicians anticoagulate such patients to prevent mural thrombi being dislodged. Cardiac transplants do not contraindicate ECT if cardiac function is normal. (Weiner ea, 2001, p. 37) Renal dialysis patients requiring ECT should have their electrolyte levels normalised and, if possible, ECT should be given on the day following a dialysis session. (Pearlman ea, 1988)

³³⁷⁵ Patients on levodopa live longer but the treatment is associated with the ‘on-off syndrome’ of abrupt swings to marked relief of symptoms (‘on’) and to total immobility (‘off’). The latter responds to ECT (maintenance treatments may be needed – subcutaneous apomorphine is an alternative treatment). ECT in these circumstances might work by inducing effects on prolactin levels or via increased dopamine receptor sensitivity. Kellner and Bernstein (1993) have made several recommendations concerning the employment of ECT in Parkinson’s disease patients: use in severe, drug-refractory cases who give informed consent and understand that the effects are transient and limited; half the dose of levodopa and stop adjunctive medication (as prophylaxis against dyskinesia and delirium); unilateral ECT is tried (switch to bilateral if no response after three treatments); stop ECT after maximum effect is achieved or after six treatments if no improvement is noted; put the patient back on his pre-ECT medication and dosages after the course of ECT; and, finally, consider maintenance ECT.

³³⁷⁶ Depending on urgency of the case.

³³⁷⁷ E.g. beta-blockers, sodium nitroprusside, and hydralazine (Tess & Smetana, 2009). One should seek neurological/neurosurgical/anaesthetist consultation. Smaller aneurysms (< 10 mm in diameter) appear to be safer than larger ones.

³³⁷⁸ Cardiac reserve should be assessed because the heart works harder during ECT. Uncontrolled cardiac failure is a relative contraindication to ECT; try to avoid ECT within 3 months, especially if severe MI.

³³⁷⁹ In fact, many cases have been treated with ECT with low rate of complications. (Hsiao ea, 1987) Tess & Smetana (2009) suggest delaying ECT for at least 1 month post-stroke and that BP should be tightly controlled to minimise hypertension (haemorrhage) and hypotension (ischaemia).

³³⁸⁰ Some clinicians use a magnet to convert a demand pacemaker to a fixed mode to prevent triggering of a pacemaker during ECT.

³³⁸¹ Delay ECT advised by Tess & Smetana (2009). They would start antihypertensive treatment if BP is 140/90 or more (unless there was a recent CVA) but they would avoid beta-blockers lest there is interference with efficacy of ECT. Stable chronic hypertension with BP of < 140/90 is managed by continuing patient’s usual antihypertensive drugs through the morning of ECT.

³³⁸² Repair before ECT to avoid ventricular overload during seizure. However, O’Reardon ea (2008) gave ECT to a 96-year-old with this condition without untoward event (ventricular ejection was normal at 70%). Tess and Smetana (2009) suggest echocardiography to assess severity of stenosis; there is some data to suggest that ECT is safe with use of short-acting beta-blockers to reduce hypertension and tachycardia during ECT.

³³⁸³ Seek ophthalmologist’s advice, avoid head movement during ECT, and consider blunting rise in blood pressure during electroplexy.

³³⁸⁴ Taking care to preserve the pacemaker function. ECT may convert atrial fibrillation to sinus rhythm.

Patients with obstructive sleep apnoea (OSA) should ideally be subjected to adequate sleep laboratory investigation (including establishment of optimal continuous positive airway [CPAP]) and the employment of measures to counteract OSA (weight loss, CPAP, mandibular advancement device, ENT surgery) before giving ECT. However OSA may be discovered during emergency use of ECT (or the aforementioned tests and treatments may not be readily available or take too much time to work) and, in such cases, lengthy ventilation with 100% oxygen should precede general anaesthesia. Additional options are insertion of a nasopharyngeal airway, night-time CPAP, mandibular advancement device and, in extreme cases, tracheostomy.(McCall ea, 2009)

Monoamine oxidase inhibitors (MAOIs)

Various authors recommend stopping them for periods ranging from 10 days to 6 weeks

Most authorities do **not** now think that MAOIs (or TCAs) contraindicate ECT (e.g. Wells & Bjorkstein, 1989; Weller, 1992; Metzger, 1999; Weiner ea, 2001; Marangell ea, 2003, p. 1124; Alpert ea, 2004, p. 257; Scott, 2005, p. 111)

Do not give sympathomimetic drugs if the patient is taking an MAOI

Fochtman ea (2003) suggest that concerns among anaesthesiologists regarding hypertensive reactions in patients on MAOIs arise from the use of indirect sympathomimetic agents during emergency surgery and they view this as being irrelevant in the case of ECT. However, the anaesthetist must be consulted. The largely North American practice of stopping antidepressants, such as TCAs, is currently 'undergoing reconsideration'.(Weiner ea, 2001, p. 89, Fochtman ea, 2003, p. 380) Stopping such drugs during a course of ECT has not been popular in these islands. The present author has (thankfully) experienced no problems combining ECT with SSRIs, TCAs or lithium (see Jha ea, 1996; Kellner & Bourgon, 1998; Stewart, 2000; Papakostas ea, 2000) and there is some evidence that suicide risk (Brådvik & Berglund, 2000) and relapse (Sackeim ea, 2001) are reduced by continuing antidepressant drugs or lithium after ECT. This author continues antidepressants as long as they were or could be helpful, especially with in-patients. Less ill out-patients might commence a new antidepressant after a course of ECT is over. Sackeim ea (2009) found that the efficacy of ECT was increased by concomitant antidepressant medication with less cognitive dysfunction than when placebo was used; however, nortriptyline was superior to venlafaxine and tended to worsen cognitive function. There have been some concerns that lithium may be associated with delirium, catatonia or prolonged seizures, although opinion is 'divergent'.(Weiner ea, 2001, p. 83; Scott, 2005, p. 111, Fochtman ea, 2003, p. 380) and Welch (2008, p. 638) states that lithium is 'usually safe'. Neither is there any good reason for stopping antipsychotic drugs during a course of ECT.(Weiner ea, 2001, p. 18; APA, 2002, p. 417; Braga & Petrides, 2005) Until more data is available, caution is suggested in patients taking bupropion because of reports of seizures in patients on high doses.

Some indications mentioned for ECT by year

- 1943. Intractable epilepsy³³⁸⁵
- 1945. Delirium
- 1950. Stauder's lethal catatonia
- 1953. Refractory delirium
- 1954. Anorexia nervosa³³⁸⁶
- 1967. Mental disorders associated with SLE
- 1972. Alcoholic delirium
- 1977. Mental disorders secondary to enteric fevers
- 1981. Phencyclidine delirium
- 1984. OCD refractory to medication
- 1987. In cases of intracranial shunt, shunt patency should be checked before ECT
- 1989. Mood congruent delusions or psychomotor retardation
- 1989. ECT used safely for major depression in AIDS.
- 1991. Catatonia secondary to a general medical disorder
- 1992. Depression in multiple sclerosis³³⁸⁷
- 1994. HIV-associated stupor

³³⁸⁵ ECT is effective for status epilepticus,(Cline & Roos, 2007) although it may also induce it.

³³⁸⁶ Series of 19 cases.

³³⁸⁷ Whilst ECT is effective in such cases, a minority, according to Krystal and Coffey,(1997) may show some neurological deterioration.

1995. Mental disorders in head injury patients

1996. Chronic pain due to affective disorders

1997. ECT can be given in presence of aortic stenosis if left ventricular function is normal

1999. NMS with psychotic symptoms (CPK range: 777-18,5000; normal = 0-70 IU/L)

2000. Eight cases in the literature where ECT was given to patients with intracranial masses, none with bad outcomes: an individual risk-benefit analysis should be performed; successful treatment of depression in the fortnight following CVA

2001. ECT in depressed patients with intracranial metal objects (e.g. shrapnel) or a metallic skull plate (place electrodes equidistant from defect)

2003. Forced normalisation as a possible indication³³⁸⁸; ECT improved depression in suspected cases (N = 7) of Lewy body dementia

2005. ECT to produce remission of tardive dystonia (blepharospasm) in a case of treatment-refractory schizophrenia

2008. Major depression with psychotic features in elderly female with advanced Parkinson's disease and in situ deep brain stimulator

2009. Bipolar affective disorder I with psychotic symptoms in Fahr disease

Complications

With adequate precautions significant problems are rare.

Possible complications

Manic/mixed state switch in bipolar depression³³⁸⁹

Headache³³⁹⁰

Myalgia³³⁹¹

Confusion³³⁹²

Amnesia

CVA

Status epilepticus³³⁹³

‘Scoline apnoea’³³⁹⁴

Aspiration pneumonia

Pulmonary embolism

TB flare up

Worsened neurological status in neurosyphilis

Subconjunctival haemorrhage

Epistaxis

Peptic ulcer bleed

Compression fractures of mid-dorsal vertebrae

Fractured limb bones

Dislocated jaw

Broken teeth

Bitten tongue

Fat embolism

Myocardial infarction, cardiac arrhythmias, angina, congestive cardiac failure

Aspiration pneumonia (rare) may be more likely in those patients who have gastroparesis due to diabetes mellitus, hypothyroidism³³⁹⁵, amyloidosis, connective tissue disorders or gastric tumours, and emptying the stomach with a nasogastric tube may be necessary prior to anaesthesia.

³³⁸⁸ The present author has used ECT successfully for this condition in a small number of cases.

³³⁸⁹ This occurs in about 7% of cases. One may either continue the ECT treatment or stop ECT and use medication to treat the mania/mixed affective state.

³³⁹⁰ May be vascular and may respond to intranasal sumatriptan, a 5-HT_{1B/1D} agonist.(Markowitz ea, 2001) However, in my experience, post-ECT headache is responsive to minor analgesics such as paracetamol. The same medication takes care of any muscle aches due to the muscle relaxant.

³³⁹¹ This responds to paracetamol. Rasmussen ea (2008b) found no correlation between myalgia following ECT and either convulsive movements or dose of succinylcholine.

³³⁹² Anticholinergic load of medication may contribute and may come from classical sources (e.g. TCAs) or less obvious ones (e.g. warfarin or prednisone).

³³⁹³ If seizure lasts > 2 minutes consider IV diazepam or more induction agent – Abrams, 1992; lorazepam is preferred by many authorities;(Weiner ea, 2001) Phenytoin or fos-phenytoin can be used if the former agents fail. The anaesthetic agent can also be used.

³³⁹⁴ Tests for pseudocholinesterase deficiency are too sensitive for screening purposes, giving many false positives.

³³⁹⁵ ECT raises TSH levels during treatment, but photherapy does not affect thyroid function tests.(Sit & Rothschild, 2002)

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If a beta-blocker³³⁹⁶ is used to control ECT-induced rises in blood pressure and heart rate it is advisable to add an anticholinergic agent such as atropine to prevent possible asystole³³⁹⁷. Some authorities use labetalol (Trandate), a short-acting blocker of both alpha and beta receptors, to prevent tachycardia. Nifedipine (Adalat), a calcium channel blocker given sublingually before anaesthetic induction, has been used in at-risk cases to prevent excessive rises in blood pressure during ECT.

Postictal delirium affects a minority of patients and usually abates in much less than an hour. It may occur with one or all treatments. Reassurance, gentle restraint, nursing in a quiet area, and, when necessary, medication (diazepam, midazolam, haloperidol) are the basis of management. Promethazine 25-50 mg orally two hours before ECT may prevent post-ECT agitation.(Vishne ea, 2005) A reduction in the electrical dose or frequency of ECT treatment may be required.

Postictal delirium

Agitation
Disorientation
Uncooperative with staff
Amnesia for the episode (usually)

Insulin requirements before and after ECT were not significantly altered in one study of diabetics.(Netzel ea, 2002) One approach is to hold the morning dose of insulin until after the treatment.(Welch, 2004, p. 107) Tess & Smetana (2009) suggest measuring blood glucose pre- and post-ECT, giving 50% of the usual dose of long-acting insulin the morning of ECT, withholding oral agents until the patient can eat, giving short-acting insulin to correct increases in blood glucose, and giving ECT early in the morning if possible. Burns, usually superficial, should be very rare. Rarely one may encounter unilateral (Mason, 1955) or bilateral (O'Shea ea, 1996; O'Shea, 2001) foot drop for which many theories have been proposed, e.g. pressure on the common peroneal nerve when the patient is held down under anaesthesia. Maximum output from an ECT machine delivers a current that could raise brain temperature by 10% of a degree centigrade. This is insufficient to cause electrical injury³³⁹⁸.(Swartz, 1989)

Mortality

Deaths are most often attributed to cardiovascular and cerebrovascular mechanisms.

ECT and death

Early Danish study - 1 death/22,000 treatments
1981 RCPsych (RCPsych) report - 1 death/2,600 courses (a course consisting of an average of 5-6 separate treatments; 8-9 for major depression in USA: Weiner ea, 2001)
1994 RCPsych estimate - 1 death/50,000 treatments (same figure as Fink, 1978)
ECT is 10 times safer than having a baby in the USA
Weiner ea (2001) - mortality rate from ECT declined over the years; suggested that it is currently likely to be 1/10,000 patients and 1/80,000 treatments
Lightening kills 6 times as many Americans as does ECT
Death rate from ECT estimated to be less than spontaneous death rate in USA (Abrams, 1997)

Nuttall ea (2004) conducted a review of ECT at the Mayo Clinic³³⁹⁹. 2,279 patients received 17,394 ECT treatments between 1.1.1998 and 31.12.2001 (median number of applications of ECT/patient = 7). 21 patients (> 1%) experienced complications during the first series of ECT treatments (mostly cardiac, especially arrhythmias), none leading to permanent sequelae. No one died immediately after ECT. 18

³³⁹⁶ Some authors avoid beta-blockers because of a couple of reports that it reduces the efficacy of ECT by shortening seizure duration.

³³⁹⁷ Asystole has been reported in resistant depression treated with venlafaxine (>300 mg/day) ECT and using propofol.(Gonzalez-Pinto ea, 2002)

³³⁹⁸ In cardioversion 200-400 joules are delivered in a second, and may be repeated. Typically, ECT requires 40-50 joules (max 110 joules) delivered over a number of seconds.(Maixner & Taylor, 2008, p. 72)

³³⁹⁹ Rochester, Minnesota.

people died within 30 days of the final treatment, “none related to ECT” (suicide, lung abscess, stroke, cancer, etc). The authors concluded that ECT was extremely safe.

A Danish study (Munk-Olsen ea, 2007) compared inpatients that had and had not received ECT: death from natural causes was reduced in those receiving ECT but they had a slightly higher suicide rate (especially in the first week after ECT).

Elderly

Old age as such does not preclude ECT (O’Shea ea, 1987; Tomac ea, 1997; Gormley ea, 1998; Tew ea, 1999; Scalia ea, 2007; O’Reardon ea, 2008) although confusion may last longer following ECT. This author normally gave ECT thrice weekly except in the elderly where he gave it twice weekly³⁴⁰⁰. There is some evidence that a thrice weekly frequency may be superior in terms of speed of clinical response.(Sackeim, 2003, p. 538) Recent guidance on optimal ECT frequency for the generality of patients is ‘twice per week’ and ‘probably twice per week’ for bilateral and unilateral ECT respectively³⁴⁰¹.(Scott, 2005, p. 141) It is the present author’s experience that it is wrong to stop ECT if in the middle of a course the patient becomes confused, the depression has not yet lifted, and there is no other cause for the confusion (e.g. infection). Access to physiotherapy is important when giving ECT to old people or those with low respiratory reserve. Higher dose of muscle relaxant than usual may be needed in cases with osteoporosis. Although data is scarce, Andrade ea (2007) suggest that (at least younger) schizophrenic patients are not at increased risk of fracture from ECT. Elderly and arthritic patients may require spinal X-ray films before ECT.

Bowley and Walker (2005) suggestions:

ECG - cardiovascular disease, irregular pulse, heart murmur, hypertension, respiratory or kidney disease, diabetics aged over 40 years, and anyone over 50

Chest x-ray - suspected chest infection, cardiomegaly, congestive cardiac failure (CCF), pulmonary embolism, suspicion of fractured ribs (e.g. after a recent fall)

Association of Anaesthetists of Great Britain and Ireland (2000) require (mandatory):

Automated non-invasive blood pressure monitoring

ECG

Pulse oximetry

End-tidal carbon dioxide

More treatments are cancelled because of failure to fast (including sips of water) than through physical illness.(Bowley and Walker, 2005, p. 125)

Repeated courses of ECT, or even maintenance ECT³⁴⁰², may be necessary where maintenance pharmacotherapy does not prevent relapses.

Pregnancy

The Irish MHC (2006, 2009b) mandate that all pregnant patients be assessed by an obstetrician before receiving ECT, that resources are available to handle emergencies in mother and baby, and that foetal monitoring is used if the first trimester has passed. Aspiration is more likely in pregnant than in non-pregnant patients. Weiner ea (2001) suggest that a wedge be placed under the patient’s right hip if the pregnancy is greater than 20 weeks duration in order to displace the womb from the great vessels. The antimuscarinic glycopyrrolate³⁴⁰³ appear to be relatively safe during pregnancy whereas atropine causes foetal tachycardia, variable heart rate, and may mask foetal distress. Sodium citrate may be used to reduce the risk of gastric regurgitation. ECT does not precipitate labour. Succinylcholine does not cross the placenta. The uterus is not involved in the muscle contractions of the seizure.

Mechanism of action

The antidepressant action of ECT increases with each application until a plateau is reached.

³⁴⁰⁰ The usual frequency of ECT is twice weekly in Britain and thrice weekly in the US.

³⁴⁰¹ In practice it is a trade off: twice weekly + slower response or thrice weekly + cognitive problems.(Kay & Tasman, 2006, p. 926)

³⁴⁰² Every 1-4 weeks, depending on individual response.

³⁴⁰³ Used, e.g., as topical cream for excess sweating in cases of diabetic autonomic neuropathy.

Possible mechanisms

Animal studies - ECT causes an increase in post-synaptic receptor sensitivity (see O'Shea ea, 1983)³⁴⁰⁴

Virtually all neurotransmitter systems are affected by ECT

Enhanced serotonergic responsivity - increase in fenfluramine-induced plasma prolactin levels after ECT; increases in CSF 5-HIAA and HVA; increase in plasma tryptophan

Stain-Malmgren ea (1998) stated that there may be an increase in platelet 5-HT₂ receptor density in drug-refractory depressives following ECT, i.e. up-regulation of such receptors, an effect opposite to that associated with antidepressant drugs, which downregulate 5-HT₂ receptors. Yatham ea (2010) reported a decrease in brain 5-HT₂ receptors in depressed individuals following ECT, an effect similar that caused by antidepressant drugs, and the authors suggest that ECT's ability to down-regulate brain 5-HT₂ receptors in drug-resistant depressives may explain its efficacy in such cases.

Decreased melatonin production

Many antidepressant drugs, and ECT, are known to downregulate postsynaptic beta-adrenergic receptors

Platelet alpha-2-adrenoceptors appear to be supersensitive in depression, and ECT seems to downregulate these receptors (Werstik ea, 1996)

Fall in plasma noradrenaline levels may be associated with improved depression ratings in DSM-III-R melancholic or psychotic depression (Kelly & Cooper, 1997)

No association between non-suppression on DST and either immediate outcome or outcome at 6 months after ECT (Scott, 1998)

Whilst ACTH and plasma cortisol levels may rise acutely following ECT these levels may fall during the course of ECT, suggesting down-regulation of HPA axis (Grunhaus ea, 1987)

A relatively post-ECT high afternoon plasma cortisol level might increase risk of relapse (Cooper ea, 1995)

ECT may work by increasing brain-derived neurotrophic factor (BDNF) levels, a neuroprotective agent that promotes neuronal growth and synaptogenesis³⁴⁰⁵ (Reid, 2005; Taylor, 2008)

Neuropeptide release may also be therapeutic. ECT might act by augmenting inhibition by TRH and related peptides of hyperactive glutamatergic subcortical limbic neurones in depression

ECT may affect G-protein coupling to receptors, activity of adenylyl cyclase and phospholipase C, and the regulation of ionic calcium into nerve cells

Cerebral blood flow is increased immediately with ECT³⁴⁰⁶, followed by postictal hypoperfusion - the latter persists after a full course of ECT, and the degree of acute reduction in blood flow, especially in the frontal cortex, may predict response, non-responders showing no decline in flow (Trimble, 1996)

Anticonvulsant drugs are used as mood stabilisers and ECT increases the seizure threshold.³⁴⁰⁷ An anticonvulsant action may be important for the therapeutic potential of ECT, perhaps by augmenting glutamate-mediated synaptic transmission in the hippocampus by neuropeptide Y. Azuma ea, (2007) using 30 consecutive depressed in-patients who had not responded to standard medication, gave bilateral ECT in either sine or pulse wave mode and examined EEG parameters: postictal suppression was the only significant predictor of treatment outcome when baseline HAM-D and mode of stimulation were controlled for. Fink ea (2008) reported on 80 patients receiving continuation treatments after successful ECT: seizure threshold did not change in 70%, increased in 21%, and fell in 9% at remission, i.e. seizure threshold did not rise conclusively with remission; whilst results failed to support the anticonvulsant hypothesis for ECT the authors admit to 'numerous limitations' in procedures that may have limited their findings, e.g. seizure threshold was not measured for a week after the end of treatment.

³⁴⁰⁴ A refractory hallucinating patient on IM haloperidol decanoate developed EPS immediately following the seizure and stopped hallucinating. It should be noted that increased blood-brain barrier permeability is increased by ECT but returns to baseline within 24 hours. (Maixner & Taylor, 2008, p. 72)

³⁴⁰⁵ A number of studies indicate that electroshocks (ECS) increase synaptic connectivity. Chronic ECS more than single ECS causes mossy fibre sprouting and neurogenesis in hippocampus.

³⁴⁰⁶ Cerebral blood flow during ECT (using PET) for depression increases chiefly in basal ganglia, brain stem, diencephalon, amygdala, vermis, and frontal/temporal/parietal cortex – soon after ECT it increases in thalamus and decreases in anterior cingulate and medial frontal cortex. (Takano ea, 2007)

³⁴⁰⁷ Rasimas ea (2007) found that women had longer seizures than men (but only at first treatment session), that there was a strong inverse correlation between age and seizure length, and that the only significant drop in seizure duration was between the 1st and 2nd treatments, seizure duration remaining relatively constant thereafter.

In 10 people with psychotic depression given ECT, PET showed that relief of depression was associated with increased metabolism in the left subgenual anterior cingulate gyrus, and antipsychotic action correlated increased left hippocampal metabolism.(McCormick ea, 2007)

Cytokines IL-1 β and IL-6 are released after ECT, possibly due to neuronal depolarisation.(Lehtimäki ea, 2008)

Increased access to remote episodic memories, so aiding re-establishment of personal identity.(Frais, 2010)

In a small study (7 males, 2 females), inhibiting synthesis of both noradrenaline (using alpha-methyl-p-tyrosine) and serotonin (using tryptophan-free amino acid mixture) following successful treatment of major depression with ECT led to no significant changes in depression scores casting doubt on the theory that catecholamine and (the indoleamine) 5-HT availability is necessary for maintaining the initial antidepressant response to ECT.(Cassidy ea, 2010)

Three basic designs have been used to show that ECT works: controls given anaesthetic but no ECT, controls given nothing at all, and ECT compared with other treatments. Brill ea (1959) found repeated induction of unconsciousness to be as effective as real ECT. However, only 16 of 97 patients were depressed. The remainder of this mostly chronic group was suffering from schizophrenia or schizoaffective disorder.

Seizure activity in the brain is necessary for the clinical effectiveness of ECT.(Brandon ea, 1984; Freeman ea, 1978; Johnstone ea, 1980) Lambourn and Gill (1979) did not find real ECT better than sham ECT but their methodology has been criticised.(Weiner ea, 2001) A meta-analysis confirmed that ECT is superior to medication and simulated ECT.(Kho ea, 2003) The important component of the seizure is the *clonic* phase, and a jerk produced by the current should not be mistaken for a fit. Some authors (e.g. Malitz & Sackeim, 1986) and many clinicians believe that higher doses of electricity are more effective than lower doses despite the fact that both produce a seizure.(Dubovsky ea, 2003, p. 496) Also, simply having a generalised fit of adequate generation may not be sufficient to treat depression: the dose of electricity and the electrode positioning appear also to be important.(Sackeim, 2003, p. 536)

The seizure

The fit is equally effective no matter if just enough energy or more than enough energy is used to induce it. Therefore use the minimum amount of electrical energy required to induce a convulsion. One can reduce the amount of energy by a perpendicular rise and/or fall in stimulus amplitude to maximise the amount of energy transmitted at peak amplitude. An ECT instrument should be used which generates a discontinuous pulsatile waveform rather than a continuous sine wave³⁴⁰⁸. Constant current, brief pulse equipment giving a train of voltage pulses constitutes a more satisfactory physiological stimulus. An Indian study found that lower (50 pulses/second) was more efficient in inducing a seizure than was a higher (200 pulses/second) stimulus pulse frequency (the lower frequency caused a greater reduction in seizure threshold) and there were no significant cardiovascular responses between the two frequencies.(Girish ea, 2003) Most modern machines produce a uniphasic (one direction only) or biphasic brief-pulse current.³⁴⁰⁹ The ECTRON series 5 (a constant current apparatus) delivers an average effective stimulus of about 275 mC (Millicoulombs) over 3.25 sec. The stimulus intensity (i.e. mC/sec.) is therefore only about one-sixth that of the sine wave stimulus.

An 'adequate' seizure (on EEG) is said to last 25-30 (some say 20-50) seconds, although this author has seen many patients recover with much briefer seizures,(see Nobler ea, 1993; Kales ea, 1997) and there is increasing consensus that seizure duration is not be related to the efficacy of ECT.(Sackeim ea, 1991; Weiner ea, 2001, p. 83; Dubovsky ea, 2003, p. 496; Whitehouse & Scott, 2005, p. 161) As noted by Barnes,(2005) 'shorter seizures may be acceptable if the patient remains well'. Kho ea (2004) found that high seizure energy index³⁴¹⁰ predicted rapid response in major depression. Until this debate is resolved seizure duration of at least 15 seconds is desirable. EEG seizure activity is often of greater duration than observable motor convulsive activity. Non-convulsive seizures or status epilepticus may only be seen on the EEG. The EEG tracing may contain a lot of muscle artefacts³⁴¹¹ and suxamethonium-induced twitching

³⁴⁰⁸ A practice that, unfortunately, has not entirely caught on.(Sienaert ea, 2005)

³⁴⁰⁹ Today's ECT machines deliver very brief (1-2 msecs) pulses (< 70 pulses/sec) of direct current in series.

³⁴¹⁰ Mean integrated amplitude x seizure duration.

³⁴¹¹ Including those caused by the anaesthetist, e.g. when applying a face mask.

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may be mistaken for the clonic phase of the seizure.³⁴¹² A successful ECT shows responses on the EEG tracing over both hemispheres³⁴¹³ indicating generalisation. The disparity between seizure adequacy as measured by observed motor activity or EEG activity is probably small.(Ratthalli ea, 2009)

Typical EEG response to ECT (chronology)

Latent phase - low amplitude, high frequency, polyspike activity

Increase in amplitude of polyspike activity and progressive slowing

Clonic phase

3 Hz spike and wave pattern

Progressive loss of spike and wave activity

Termination of seizure activity usually indicated by suppression: greatly attenuated activity following the high-amplitude sharp and slow seizure activity

Seizures with unilateral ECT are asymmetrical with higher ictal EEG amplitudes over the stimulated hemisphere than over the other hemisphere. Theophylline, an adenosine antagonist like caffeine, can prolong seizures in a patient undergoing ECT (as can caffeine, aminophylline, and several other drugs, incl. SSRIs), sometimes seriously so, but its use is confined to the research arena. When maximum electrical stimuli fail to produce a seizure ('missed or abortive seizure') etomidate (or possibly ketamine³⁴¹⁴) may be employed.(Patel ea, 2006) Hydration and hyperventilation are also useful strategies.(Datto ea, 2002; McCall, 2002) Electrode handsets with both electrodes joined onto a single stem have the electrodes placed far too close together. Shorting may occur due to excess scalp moisture and may be a reason for lack of a seizure. Rarely (Weiner ea, 2001, pp.19, 88) clozapine causes a prolonged seizure.(Bloch ea, 1996)

Procedure

A firm surface and private surroundings are required, as are assistants to hold the patient down at the shoulders and pelvis. An oxygen source (brain oxygen requirements increase during a seizure; oxygen lowers seizure threshold, i.e. amount of electrical energy needed to produce a grand mal seizure; and the fall in pCO₂ lengthens the duration of the seizure), Ambu bag, mouth gag and suction apparatus should be available. 100% oxygen is given before and after induction of the seizure. Hyperoxygenation does not harm the patient with chronic chest problems when given for brief periods only.

If the patient fails to have a good seizure after the initial stimulus, then the patient should be hyperoxygenated and consideration should be given to whether the settings on the machine should be increased by, say, 25% – but poor electrode contact with the scalp is the commonest culprit!

Interestingly, the APA Task Force on ECT (Weiner ea, 2001, p. 130) does not recommend the use of a plastic airway³⁴¹⁵ because of a perceived risk of dental or jaw injury. Instead they suggest the use of a bite-block.³⁴¹⁶

The dose of electricity is described in units of charge (Coulombs) rather than energy (Joules) because the former is independent of the variable impedance of patients and is more closely related to both the desired therapeutic and the unwanted cognitive effects. Ohm's law states that voltage = current x resistance; voltage varies as a function of resistance/impedance³⁴¹⁷. A constant current is recommended. Constant voltage or constant energy devices are not recommended.(Weiner ea, 2001) The convulsion is usually induced using a machine with automatic timing and a choice of waveforms. The minimum stimulus needed

³⁴¹² The initial tetanic stimulation of the masseter by the electrodes should not be mistaken for less than adequate muscle relaxation..

³⁴¹³ Therefore use two electrodes, one over each hemisphere.

³⁴¹⁴ There is some evidence that ketamine may cause less cognitive problems than other anaesthetics.(MacPherson & Loo, 2008)

³⁴¹⁵ E.g. Guedel.

³⁴¹⁶ The present author's former centre has employed a Guedel-type airway for years without adverse results. This author also remembers seeing psychiatrists using the heel of a shoe as a bite-block! Whatever is used there should be no sharing of the same item by patients.

³⁴¹⁷ Increased impedance necessitates an increased voltage to maintain a constant current.

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to produce a generalised convulsion is applied, e.g. 140 volts for half a second. Passage of the stimulus should be accompanied by an audible or visual signal.³⁴¹⁸

A typical good ECT suite consists of waiting, treatment and recovery. Staff should be friendly, expert, and known to the patient. Piped music³⁴¹⁹ may help to calm a nervous patient.

Atropine

May or may not be given before anaesthesia

Given subcutaneously, atropine will not block the vagus and will simply dry the mouth

Usual dose (0.3-0.6 mg sc or 0.4-1.0 mg IV) gives some degree of vagal blockade but unreliable reduction in secretions

May exacerbate post-seizure hypertension and tachycardia

Large doses may cause confusion or psychosis, and uncomfortable dry mouth

Glycopyrrolate

0.2-0.4 mg IM, SC, or IV)

Does not cross blood-brain barrier

Dries secretions

Does not cause psychiatric symptoms

Leaves blood pressure unaltered

Attenuates deoxygenation and extreme bradycardia due to acute effect of ECT (Rasmussen ea, 2007)

Caffeine pretreatment is not recommended.(Scott, 2005, p. 113)

Resistance (impedance) is increased in line with skull thickness. Using information from a skull x-ray, it has been suggested that one place the electrodes over the thinnest part of the skull. Skin resistance must be reduced with a salt-water solution or electrojelly³⁴²⁰ rubbed into the area where the electrode pad is to be placed. Then an IV anaesthetic is given.

Dose titration (stimulus dosing)

Technique for determining correct amount of electricity required for a bilateral seizure

When using 'test' facility on ECT machine the apparatus is in test mode, i.e. it passes a small amount of electricity between the electrodes and informs about the static impedance of the head - if it is too high it is likely that the dynamic impedance is also too high, i.e. the machine will be unable to deliver the correct amount of electricity to the patient

Static impedance will be high if there is poor contact between electrodes and scalp

Electrodes should not be moved prior to delivering ECT after using the 'self-test' facility because the operator may significantly alter static impedance

Thiopentone (thiopental) causes a prolonged sleep (slow recovery) whereas methohexitone sodium has less anticonvulsant effects and has a lesser tendency to induce cardiac arrhythmias³⁴²¹. Methohexitone is associated with quick induction and recovery and was recommended by the RCPsych (RCPsych' Special Committee on ECT, 2002) and by Laidlaw (1995), but availability has been compromised; the dose is 0.75 mg/Kg; seizure threshold is increased at doses over 1.5 mg/Kg with the potential for non-therapeutic seizures. Methohexitone sodium (Brietal) was withdrawn from the Irish market in 1999, and it later became unavailable in the USA.(Kellner, 2003)

Propofol³⁴²² infusion syndrome

³⁴¹⁸ It should be noted that, unlike the situation in the USA, European machines are capable of high output, i.e. > 576 mC.(McCall, 2002) This is because the FDA limits the electrical output of ECT machines, a measure with particular implications for unilateral ECT.(Maixner & Taylor, 2008, p. 63)

³⁴¹⁹ Classical and soft.

³⁴²⁰ Similar to the jelly used for an ECG.

³⁴²¹ It should be noted that Rosa ea (2007) found no difference between etomidate, propofol, and thiopental when used as anaesthetics with ECT.

³⁴²² Causes of green/blue urine include propofol, biliverdin, pseudomonas UTI, Hartnup disease, cimetidine, amitriptyline, methylene blue, indomethacin, and food colouring.(Leclercq ea, 2009)

Various cardiac dysrhythmias
 Metabolic acidosis
 Hyperkalaemia
 Rhabdomyolysis
 Acute heart failure

In fact, postictal dysrhythmias may be less common with propofol than with thiopental. (Bowley & Walker, 2005) Controversially, (Laidlaw, 1995) the RCPsych opposed using propofol (Diprivan) in 1994 because of a tendency to increase the seizure threshold (Nally, 2002; Datto ea, 2002; but see Scott & Boddy, 2002; Geretsegger ea, 2007) or shorten the duration of seizures,³⁴²³ although these may not affect therapeutic outcome³⁴²⁴. (Fear ea, 1994; Datto ea, 2002; Scott & Boddy, 2002; Bauer ea, 2009) and it may be useful in patients who experience prolonged seizures from ECT and to minimise post-ictal nausea and vomiting. (Bailine ea, 2003) The findings of Okonkwo ea (2005) and Bauer ea (2009) suggest that propofol use may necessitate the employment of a somewhat higher dose of electricity that that needed when thiopentone³⁴²⁵ is used, and Patel ea (2006) report longer ECT courses with propofol than with etomidate. Also, the number of ECT applications per course may be increased. Scott & Boddy (2002) found no difference between propofol and methohexitone in terms of the median number of treatments (8) or the median initial seizure thresholds (75 mC) within courses. Nevertheless, propofol should be avoided in paediatric populations because of concerns raised over deaths in American ICU patients.³⁴²⁶ Not only does propofol reduce seizure length³⁴²⁷, it also reduces the extent of haemodynamic change accompanying ECT, e.g. blood pressure rises less than with methohexitone/methohexital. (Geretsegger ea, 2007) Addition of the ultra-short-acting opioid remifentanyl to propofol³⁴²⁸ reduces the required dose of the latter and increases the postictal suppression index³⁴²⁹. (Porter ea, 2008c) Rasmussen ea (2009) found³⁴³⁰ no real increase in seizure length when remifentanyl was added to thiopental, a finding echoed by Nasser ea. (2009) Concern has been raised concerning abuse of propofol, despite its narrow therapeutic index, by US healthcare professionals, sometime with fatal results. (Charatan, 2009) Abuse leads to a dissociative state with euphoria. Propofol was implicated in the death of singer Michael Jackson in 2009. As pointed out by Hartle and Malhotra (2009), the drug is safe when used for legitimate reasons.

Etomidate may increase seizure duration, increase extraneous muscle movements, cause local pain at the injection site, and rarely induce adrenocortical dysfunction after repeated dosing. (Benbow ea, 2002) Stadland ea (2002) and Khalid ea (2006) suggest switching from propofol to etomidate if seizure duration is too short or seizure threshold is very high. The importance of seizure duration on the effectiveness of ECT is not now seen as being of such great importance as it was in the past (Weiner ea, 2001; RCPsych Special Committee on ECT, 2002) and, indeed, etomidate has been accused of prolonging seizures! (RCPsych' Special Committee on ECT, 2002) Also, Erdil ea (2009) found that the QT interval was shortened by propofol and lengthened by etomidate and propofol controlled the haemodynamic response better during ECT than did etomidate. A muscle relaxant is given after the anaesthetic via the same needle. The most commonly employed drug is the depolarising agent succinyl choline³⁴³¹ (Scoline) e.g. 25-40 mgs³⁴³². This should be drawn up late to avoid decay.

With depolarising muscle relaxants like succinylcholine, the button is pressed when muscle fasciculation³⁴³³ has **stopped**, e.g. at the chin or legs.

The most common sites for EEG recording during ECT are frontal-frontal³⁴³⁴ or frontal-mastoid montages.

³⁴²³ Measured 'from the end of electrical stimulation to the end of generalised convulsive muscular activity' by Scott & Boddy. (2002)

³⁴²⁴ Having to employ a higher electrical charge might increase the likelihood of cognitive dysfunction.

³⁴²⁵ Ingram ea (2007) found thiopentone to be associated with greater efficacy and less cognitive dysfunction when given with ECT to depressed patients (n = 30).

³⁴²⁶ The latter was to be investigated by AstraZeneca. (Irish Medicines Board, 2001)

³⁴²⁷ By up to 63% compared with methohexital.

³⁴²⁸ Or to methohexital for that matter. (Porter ea, 2008) If the clinician wishes to prolong a seizure he/she might consider using methohexital or short-acting opioid plus propofol. (Hooten & Rasmussen, 2008)

³⁴²⁹ Which might increase clinical response.

³⁴³⁰ Retrospective study of 56 cases.

³⁴³¹ Suxamethonium chloride.

³⁴³² Higher doses would obscure any clinical observation of seizure activity.

³⁴³³ Caused by the muscle relaxant.

³⁴³⁴ Frontal = at least one inch above midpoint of eyebrow.

Seizure threshold increases during a course of ECT by about 80% requiring, for example, an increase in mC requirement of 200 to 360.

Seizure threshold

Increased

ECT (bilateral > unilateral)

Males

Elderly

Reduced

Children and adolescents (Kellner ea, 1997)

Weiner (1994) suggests that the charge should exceed threshold by 150-250% and 50-100% for unilateral and bilateral ECT respectively. A stimulus just above threshold is less likely to be therapeutic than a higher intensity stimulus (especially with unilateral ECT), although very high intensities are more likely to cause adverse cognitive effects.

Excessive dose of an induction agent³⁴³⁵ will shorten seizure duration. BZDs, L-tryptophan, and centrally acting beta-blocking drugs may abbreviate a seizure. The time-honoured practice of giving one or two extra treatments after recovery is controversial but still practiced. The evidence does not support this practice. (Sackeim 2003, p. 538) ECT should be certainly stopped if a manic swing is discerned.

A post-ECT recovery suite should be available where the patient is nursed in the recovery position.

Preparation and after-care is the same as for any operation involving a general anaesthetic.

*Hamilton cuff method*³⁴³⁶

Sometimes used to ascertain that a fit has occurred

Blood pressure cuff is inflated well above systolic pressure (on the same side as the electrodes in unilateral ECT) after the anaesthetic is given and before the muscle relaxant is administered

Convulsive movements may be seen in the isolated arm

Opinion is divided its usefulness (Wise ea, 2000)

Physiological changes following ECT

After the first treatment there is a short period of episodic delta (δ) activity on the EEG. As the course progresses delta activity may become continuous with the addition of some theta (θ) waves. Persistence of prefrontal δ and θ activity may be associated with a good response to ECT. (Sackeim ea, 1996) After about 2-3 months from the time of the last treatment all patients will have normal EEG patterns, earlier for unilateral than bilateral ECT. Normalisation may only take a few days in some people, especially if they have received unilateral treatment.

ECT and sleep

Increased REM sleep

Decreased REM latency

Decreased total sleep time

If atropine is not used to block vagal activity there will initially be a bradycardia whilst the current is being passed and during the seizure which follows. This is due to vagal slowing of the heart and is followed, over the next 2-3 minutes, by a tachycardia. If atropine premedication is given there will be no slowing of the pulse and a lesser degree of tachycardia. Blood pressure changes mirror alterations in pulse rate. Routine premedication with a benzodiazepine should be avoided.

The circulation of blood in the brain increases tremendously during either a spontaneous fit or ECT.

Animal studies, where electric shocks are used to induce fits, have shown a great increase in the

³⁴³⁵ Especially propofol.

³⁴³⁶ This should not be used in people with sickle cell disease because sickling will occur distal to the inflated cuff. Also, care is required in the presence of other problems, such as peripheral vascular disease. It is important that the cuff pressure is well above systolic pressure because this rises during the seizure.

permeability of the blood brain barrier to a number of substances (e.g. horseradish peroxidase) while blood pressure is raised.(Duncan & Todd, 1991)

ECT and neurochemicals

Rapid rise in the serum cortisol for a few hours after ECT

Most, but not all, pituitary hormones increase in the plasma after ECT

Prolactin is the hormone most consistently and extensively released in response to ECT (bilateral > unilateral)

Although growth hormone is often elevated after noxious stimuli it is unresponsive to ECT and levels may even fall (these findings do not seem to be due to general anaesthesia)

Oestrogen-stimulated neurophysin (ESN) has no known physiological function but its plasma concentration provides an accurate guide to oxytocin release with the advantage of easier detection and a longer half-life.

Unilateral v bilateral

Unilateral treatment is given to the non-dominant hemisphere.³⁴³⁷ In practice unilateral ECT is nearly always given over the right cerebral hemisphere. Bilateral electrodes are placed in the bifronto-temporal position³⁴³⁸. Unilateral electrodes may be placed in a number of positions³⁴³⁹ but the recommended position is for the first electrode to be placed as for bilateral ECT and the second electrode to be placed just ipsilateral to the midline near the occiput.³⁴⁴⁰ The electrodes should be large enough not to cause a focal fit and wide enough apart to cause a generalised seizure. Firm contact is mandatory.³⁴⁴¹ A second person's help is needed when giving unilateral ECT: the head needs to be turned to the side so as make the parietal part of the head available and the head should be rested on a pillow.

Slightly more unilateral than bilateral treatments may be required in order to achieve a similar level of symptom relief. However, Sackeim *et al* (2000) found an equal response rate (65%) from *high dose* right unilateral ECT and bilateral ECT, and cognitive side effects were less with the former electrode settings. Memory impairment and post-ictal confusion are less pronounced with unilateral than with bilateral ECT. It was originally believed that right-sided ECT gave a better antidepressant effect but the same effect, from this viewpoint, is probably achieved no matter which hemisphere receives the treatment. Horne *et al* (1985) randomly assigned depressed patients to either bilateral or unilateral ECT on a double-blind basis and controlled seizure length by EEG. When seizures lasted less than 25 seconds in duration ECT was immediately given again. Both groups improved equally. If ECT had not been given again in these cases then the unilateral ECT group would have had significantly more missed seizures. Memory loss was obvious in the bilateral group but was not apparent in the nondominant unilateral group. Detailed examination of memory in severe depression before, during and after bifrontotemporal ECT (last assessment at 1 month post-ECT) using the CANTAB battery (Falconer *et al*, 2010) found significant impairments in visual and visuospatial memory during ECT and for the week following ECT, most impairment resolving within 4 weeks post-ECT, but significant impairment in spatial recognition memory were still there at the end of the study. It would be worth following up these patients (N = 24) to see if such problems persisted further and whether affected patients were at risk of relapse. Severely depressed patients who are treated without ECT should ideally be studied over the same time course for comparison purposes. On balance, the RCPsych (1995) favoured bilateral over unilateral ECT, but seemed to change its mind later.(Scott, 2005) From a purely practical point of view, one is surer of what one is doing and what one expects to achieve with the bilateral option (Kellner & Fink, 2002) and, as stressed by Copolov and Mitchell (2007, p. 575) one should not dispense with ECT before trying bilateral treatment. Maixner and

³⁴³⁷ **Methods of finding dominance** include unilateral ECT (first few treatments given on alternate sides – test verbal facility after recovery – less pronounced problems when given on non-dominant side), EEG (greater α rhythm suppression in dominant hemisphere during verbal thought), dichotic listening and visual techniques (simultaneous presentation of different, neutral information to both ears or visual fields – information presented to side opposite to dominant hemisphere is better received), handedness (ask a patient to catch a ball, use a scissors or eating utensils), position of holding a writing implement and injection of sodium amytal into the carotid artery on one side (**Wada test**: temporary speech loss when injected ipsilateral to dominant hemisphere). fMRI may eventually replace the Wada test.

³⁴³⁸ 2–4 cm above the midpoint of a line drawn between the lateral canthus of the eye and the external meatus/tragus of the ear.

³⁴³⁹ E.g. the Lancaster position.

³⁴⁴⁰ Or 4 cm on the right side of the head along a coronal line joining the tragi of the ears.

³⁴⁴¹ See RCPsych' Special Committee on ECT (1994) and Scott (2005) for further details.

Taylor (2008, p. 73) concluded that cognitive gains are insufficient to favour unilateral over bilateral ECT. If the patient fails to respond to unilateral ECT, try bilateral treatment. (Rosa ea, 2006) In one postal questionnaire study, Scottish psychiatrists (61% response rate) viewed bilateral ECT as more effective than unilateral ECT and placed remission ahead of other considerations. (Brown, 2009)

Predicting response

The more chronic the depression the less response is to ECT. ECT but not elective cholecystectomy increases ESN levels. It was suggested that a significant rise in ESN levels following ECT might predict recovery from depressive illness. (Scott, ea, 1986) Cooper ea (1985) found a fall in plasma noradrenaline following ECT was associated with improvement in depression. Depressed patients show a rise in blood glucose and plasma insulin levels after each treatment; insulin but not glucose response attenuates over the treatment course; and greater attenuation of insulin response at the fifth (final) treatment may predict relapse. (Williams ea, 1992) According to Devanand ea (1995) higher pre-ECT plasma GABA levels may predict a good response to ECT and these levels tend to fall with ECT. However, Esel ea (2008) state that depression is associated with low serum GABA and such levels are increased³⁴⁴² with ECT! Sackeim ea (1996) reported that the induction of prefrontal slow-wave activity correlated with symptomatic improvement in major depression. Kho ea (2004) found that high baseline HAM-D score and high seizure energy index³⁴⁴³ were each associated with rapid response in DSM-IV major depression.

Memory impairment

Benbow (2005, p. 172) lists associations with adverse cognitive effects of ECT: sine-wave, bilateral ECT, high stimulus intensity relative to seizure threshold, short interval between treatments, certain drugs (like lithium), and high-dose anaesthesia. Animal studies have shown brain damage due to electroshock but the method used was different from that used in psychiatry. Animal studies also demonstrate that ECT does not produce the same behavioural or neurochemical changes as spaced multiple ECT given in clinical practice. Fraser and Glass (1980) studied 29 elderly patients, aged 64-86 years, treated with ECT and found that they all had impaired memory function *before* treatment. Plotkin ea (1985) have demonstrated that poor subjective memory is significantly related to depressive symptoms in elderly patients. Improvement in depression paralleled improvement in memory regardless of whether they received tricyclics or group psychotherapy. People who recover from severe depression have impaired cognitive function irrespective of treatment. (Brodaty ea, 2001) Severe, untreated depression has a far more deleterious effect on cognition than that caused by ECT. (Wilkinson ea, 1993) ECT reduces knowledge about the world (**impersonal [public] memory**, e.g. events in the news) compared with knowledge about the self (**personal [private] memory**, i.e. autobiographical), for recent compared with remote events, and for less salient events; bilateral ECT has these effects more than right unilateral ECT, especially for impersonal events. (Lisanby ea, 2000) The change from sine wave to brief pulse ECT has been said to reduce amnesic effects (Lamprecht ea, 2005) although it has not removed the risk entirely and, whilst memory improves with time long-term data are needed. (Ingram ea, 2008) Abraham ea (2006), in a retrospective study, reported that maintenance ECT given to patients with refractory depression who had responded satisfactorily to a course of ECT only developed 'limited and tolerable' memory difficulties. The relationship between subjective reports and objective findings are weak, although methods of testing memory may not be optimal. A systematic review of articles with patients' views after receiving ECT found that at least one-third of patients reported persistent memory loss. (Rose ea, 2003) Mood state strongly influences the nature of reports. (Prudic ea, 2000) Despite discrepancies between subjective and objective memory complaints, it is important not to ignore either perspective. (Vamos, 2008) The UK Review Group, (2003) a part of the NICE³⁴⁴⁴ report, suggested that we do not have a clear quantitative estimate of the degree of short-term cognitive impairment associated with ECT or how much it may persist following symptomatic recovery.³⁴⁴⁵ A Kentucky woman of 89 who had received at least 1,250 ECTs during life showed no evidence of brain

³⁴⁴² Plasma GABA is a useful indicator of brain GABA because nearly all GABA production occurs in the CNS. Research suggests that a proportion of (major) depressed people have decreased plasma GABA levels and that ECT may increase GABA in sub-cortex or hippocampus, but tricyclic antidepressants may not change plasma GABA levels. See Dunlop and Nemeroff (2007) for review of review of reduced dopaminergic neurotransmission in major depression.

³⁴⁴³ SEI = mean integrated amplitude x seizure duration.

³⁴⁴⁴ National Institute for Clinical Excellence (NICE) in the UK.

³⁴⁴⁵ Kellner and McCall (2003) found the tone of the UK Review Group's interpretation to be 'cautious to the point of ambivalence' and wondered if 'we are still paying the price for the [over-] enthusiasm for ECT during the 1940s and 50s'. See also Rush ea (2007) who address the APA (consider ECT early) and NICE (strict reservations that may restrict access) guidelines.

damage at postmortem. In fact, her old leucotomy lesion had shown some attempt at healing! There is no significant association between past ECT and large ventricular-brain ratios. Neither does there seem to be a relationship between the rise in blood pressure after ECT and subsequent cognitive or affective change. Semkovska and McLoughlin (2010) conducted a systematic review and meta-analysis of 24 different standardised neuropsychological tests performed pre- and post-course of ECT and found that ECT-associated cognitive deficits were temporary and that performance on most tests were better after than before the treatment. Retrograde memory function was not included in this meta-analysis.

Summary of research on ECT and memory/cognitive function

1975. Use of brief pulse stimulation (instead of sine wave) can reduce memory impairment.

1980. Some patients have continuing memory problems that appear to be explained by continuing mood symptoms or substance/alcohol abuse.

1986. Reversible and transient memory loss for the 3-4 weeks around the period when ECT was administered was the most common finding.

1990. No evidence of cognitive dysfunction on any task in depressed patients tested at least 6 months post-ECT
Treatment factors increasing adverse cognitive sequelae: sine wave (brief pulse is preferred), bilateral ECT, very high stimulus intensity, excess frequency of ECT, more than one seizure/session, concomitant psychotropics, and high doses of anaesthetics.

1991. No measurable cognitive dysfunction found at longterm follow-up of patients given several courses of ECT.

Patients with normal pretreatment cognition retained this after ECT and those with poor pretreatment cognitive function showed improvement in such function after ECT.

Prospective MRI study finds no evidence of structural brain damage after repeated courses of ECT.

1993. Brain imaging pre- and post-ECT in depressed subjects find no evidence of brain damage attributable to ECT.

High electrical dosage associated with more rapid response, and unilateral ECT associated with less severe post-ECT cognitive dysfunction.

4-year follow-up of elderly major depressives: normal cognition pre-ECT associated with stable cognition over time and pre-treatment cognitive dysfunction improved over time.

1994. Review of CT, MRI, autopsy, animal studies, cell counts, etc – no evidence of structural brain damage from ECT. Cognitive deficits are transient, although ‘spotty memory loss’ may persist for events surrounding the ECT course.

ECT did not reverse the reduced cerebral blood flow found in major depression – ECT, in fact, reduced perfusion further.

TRH infusion given after third or fourth treatment may reduce cognitive deficits in depressed patients.

Basal ganglia disease, such as Parkinson’s disease, renders the patient prone to post-ECT confusion.

1995. Patients with major depression who manifest global cognitive impairment pre-ECT and who experience prolonged disorientation in the acute postictal period may be the most vulnerable group to the development of persistent retrograde amnesia for autobiographical information.

1996. Severe depression, especially in elderly, can affect memory; tests of memory pre- and post-ECT may show improvement.

1997. Single case study (> 400 treatments): cognitive effects no greater than with acute treatment and seem to be non-progressive.

1998. No significant difference between twice and thrice weekly ECT in ‘major depression, endogenous subtype’ but faster response and greater memory impairment with thrice weekly ECT.

2000. Bifrontal electrode placement is as efficacious as bitemporal electrode placement in the treatment of major depression and it causes less cognitive impairment.

Right unilateral ECT at up to 500% suprathreshold equals effect of bilateral ECT at 150% above threshold, but with less severe and persistent cognitive effects.

Antidepressant and cognitive effects of ECT increase with rise in stimulus dose relative to initial seizure threshold, up through 8-12 times that threshold.

Bifrontal ECT may have less cognitive side effects than bitemporal ECT: note that authors recommend giving ECT at threshold level.

2003. In a study of maintenance ECT v maintenance pharmacotherapy, no difference was found in neuropsychological functioning – cognitive function remained stable during maintenance ECT.

2004. Bitemporal electrode placement may be more efficacious than bifrontal placement, but it may cause modestly greater cognitive impairment.

Depressives treated with ECT in Australia did not show a deterioration in cognitive functioning.

Quality of life and function improved within first month after ECT in people with major depression in North Carolina; improved function relates to better cognition, and better quality of life is due to improved mood.

2006. Donepezil associated with quicker post-ECT cognitive recovery.

2007. Mangaoang and Lucey suggest treating post-ECT memory problems, e.g. compensatory strategies.

Postal questionnaire sent to 89 consecutive ECT patients at St Patrick’s Hospital, Dublin; 51 (57%) response; 44 would have ECT again; 35 reported at least modest improvement; 60% complained of subjective cognitive impairment.

Unipolar depressives: Bilateral ECT mainly influenced everyday memory (small decrease), which improved significantly at 3-month follow-up; semantic memory³⁴⁴⁶ had a fluctuating but recovering (more so in elderly) course; both types of memory are influenced by age and electrode placement.

2008. Autobiographical memory impairment follows ECT, objectively improving within 6 months but subjectively being more persistent.

³⁴⁴⁶ Semantic memory is a structured record of acquired facts, concepts, and skills.

ECT used safely and effectively for agitation in Alzheimer patients (chart review) – 9 of 11 had improvement or remission of agitated behaviour; 7 cases had no noted side effects; other cases showed urinary retention (1 case), atrial fibrillation requiring cardioversion (1), increased somnolence (1), decreased cognition (1), and idiopathic mild increase in serum amylase (1).

Research on bifrontal ECT to date is inadequate because non-specific cognitive measures (e.g. MMSE) have been employed and emphasis has been put on memory which is a temporal lobe function.

Tardive seizures may relate to use of lithium, paroxetine, thioridazine, theophylline, ciprofloxacin, and beta-lactam antibiotics (including piperacillin and cefotiam) although other factors may contribute, e.g. prolonged ECT seizure, electrolyte disturbance, neurological disorder, or benzodiazepine withdrawal.

Takotsubo cardiomyopathy (stress-induced acute coronary syndrome in absence of coronary artery stenosis associated with catecholamine surge) followed ECT (diagnosed by apical ballooning on cardiac imaging that resembles takotsubo [octopus fishing pot in Japan]; the patient also had Loeys-Dietz syndrome (inherited disorder of connective tissue predisposing to aortic dissection).

2010. Bitemporal (150% seizure threshold), bifrontal (150% seizure threshold) and right unilateral (600% seizure threshold) electrode placements are effective in treating depression when electrical dose is appropriate; bitemporal gives faster antidepressant response; there is little cognitive difference between the two bilateral placements.

Left and right hippocampi increased in size on MRI after ECT was given to depressed patients who received ongoing medication – they were a mixture of resistant cases, relapse despite medication, and a minority with only 2-4 weeks of medication.

It has been suggested that piracetam³⁴⁴⁷, given as 5 mg IV before ECT, may decrease memory loss and allow quicker recovery from the anaesthetic. However, Tang ea (2002) found no significant effect with piracetam on ECT-induced memory disturbance. A multivitamin preparation given IV (e.g. Pabrinex) has also been advocated for this purpose.

There is no agreement on the best way to monitor peri-ECT cognition. Options are discussed by Porter ea (2008a) who suggest baseline testing, after the third and sixth applications, and 2-3 months post-ECT. Testing should be performed at a standard interval following treatment. A mood rating scale (e.g. MADRS) should be performed at each of these time points, as should time to reorientation. Also, a cognitive battery is to be used that looks at global cognitive function (*MMSE*), retrograde memory (*Autobiographical Memory Questionnaire – short form*), new learning (*Hopkins Verbal Learning Test*), and psychomotor speed (*Digit-Symbol Substitution*).³⁴⁴⁸ The same group (Porter ea, 2008b) used a somewhat different group of tests to look for memory problems during ECT and, unsurprisingly, found significant problems ‘as early as 3 treatments’ but with ‘no evidence that these changes correlated with longer term changes’.

Repetitive transcranial magnetic stimulation (rTMS)³⁴⁴⁹

In rTMS pulses of high voltage current passed through an electromagnetic coil held against the scalp generates a rapidly alternating electric field which induces an electric current within the brain that can depolarise neurones to a depth of about 2 cm from the coil surface. The flow of current in the brain is parallel with but in the opposite direction to the current in the coil. This procedure has been used to transiently improve movement in Parkinson’s disease, to map cortical function, to inhibit overactive epileptogenic areas, and to decrease compulsive urges in OCD (with some dissenters on OCD, e.g. Sachdev ea, 2007). Whilst there is some evidence for an anxiolytic effect with rTMS, studies conducted to date have employed many different protocols and tend to lack a placebo-controlled design. (Zwanzger ea, 2009) There is evidence of improvement in depression,³⁴⁵⁰ (Klein ea, 1999; Loo ea, 1999; McNamara ea, 2001; Schutter

³⁴⁴⁷ Piracetam-2-oxo-1-pyrrolidine acetamide, a similar molecular structure to GABA.

³⁴⁴⁸ This seems to the present author to be onerous for both patient and doctor, although Porter ea (2008) suggests that ‘relatively non-specialized staff according to local resources’ might alleviate the latter problem! A shorter form but standard form of testing is needed.

³⁴⁴⁹ **TMS:** Electricity is converted to magnetic fields which the brain re-converts into electrical currents. Tissues, including bone, resist the flow of electrical current but not the passage of magnetic fields. Such fields meet cerebral neurones with resting potentials and the flow of electrical current is induced. Because the skull is highly resistant to electrical current a high dose of electricity causes only a small passage of current in the brain and may cause heat and pain *en route*. However, magnetic fields are unimpeded by the skull and changes to electric current in the brain.

³⁴⁵⁰ Is right prefrontal or left prefrontal rTMS superior for depression? Gershon ea (2003), in their overview of rTMS, suggest that left prefrontal treatment is most likely to be antidepressant. Whilst, Loo ea (2003) found rTMS to be no better than sham treatment in the treatment of resistant major depression, Fitzgerald ea,(2003) in their double-blind, sham-controlled study, found that treatment for at least four weeks is necessary to produce clinically meaningful benefits in depressed patients. Fitzgerald ea (2006) reported efficacy for the sequential application of high-frequency left-side rTMS and low-frequency rTMS to the right prefrontal cortex in patients with treatment-resistant major depression, treatment response accumulating to ‘meaningful level’ over 4-6 weeks of active therapy. Reid ea (1998) expressed concern that depression may reappear soon after stopping treatment and wondered if maintenance therapy might be needed. Martin ea,(2003) in their review and meta-analysis, found trials of rTMS to be of low quality and to provide insufficient evidence to support the use of rTMS in the treatment of depression. Patra and Coffey (2008, p. 502) stated that trials were of low quality and were not convincing, and that statistical significance (see Milev ea, 2009) might not translate into clinical significance, but

ea, 2009) but, at least for severe depression, perhaps not as good as that for ECT (Eranti ea, 2007) and rTMS may not augment or accelerate the response to antidepressant medication. (Herwig ea, 2007) Mogg ea (2008) found no difference between adjunctive rTMS to left prefrontal cortex and sham rTMS for depression. Fitzgerald ea (2008) state that most studies of rTMS in major depression have used high-frequency treatment to the left prefrontal cortex but that low-frequency rTMS to the right prefrontal cortex also has antidepressant effects, their work supporting these findings. Left temporoparietal cortical application may benefit hallucinations in schizophrenia especially if rTMS is applied to the dorsolateral prefrontal cortex (DLPFC). A single trial suggests that rTMS may have antimanic properties. (see McNamara ea, 2001 for review) Schulze-Rauschenbach ea, (2005) in a study comparing unilateral ECT (mean 9.9 treatments, s.d. = 2.7) and rTMS (the patient could choose between them), found no adverse memory effects from rTMS. Rasmussen (2008) reviewed the literature and reported that ECT was of superior efficacy to rTMS for major depression and called for larger RCTs directly comparing ECT with rTMS. rTMS may cause scalp pain from muscle spasm, hearing loss due to loud clicks (use ear plugs), possible subtle cognitive defects, possible manic switching, and seizures. (Sherman, 1998; George ea, 1999) However, Anderson ea (2006) exposed healthy young men to high doses (12,960 magnetic pulses/day for up to 3 days in one week) of rTMS without causing significant side effects and Loo ea (2007) used rTMS twice daily safely for major depression.

Contraindications (Milev & Mileva, 2010) include pregnancy (lack of data), ferromagnetic material (e.g. aneurysm clips) in the head (mouth excepted), increased intracranial pressure, epilepsy, cardiac pacemaker, severe cardiovascular or other disease.

Magnetic seizure therapy (MST)

This is rTMS deliberately given at high dosage in order to induce seizures (under anaesthesia), albeit more focal than those induced by ECT. MST-induced seizures are however generalised but with relatively low ictal EEG amplitude and postictal suppression. MST is generally well tolerated, has less adverse effects and faster recovery of orientation than unilateral ECT. 100 Hz MST over the vertex elicits seizures in most patient whereas the same procedure applied over the prefrontal midpoint is much less likely to do so. (Kirov ea, 2008) The cognitive impairments associated with MST are similar to ECT in some ways (verbal fluency, memory for temporal order – prefrontal functions) but less in others (e.g. memory for recent events and category fluency – temporal lobe). (Mantovani ea, 2008, p. 88) Further work is required to measure its antidepressant efficacy.

Transcranial direct current stimulation (tDCS, direct current polarisation)

This non-invasive method of electrically polarising cortical cells delivers a direct current (1-3 mA) via scalp electrodes. Cortical function is increased and decreased by anodal and cathodal stimulation respectively. Non-synaptic modulation of resting membrane potentials (involving NMDA among others) is the proposed mechanism of action. Changes in cortical excitability continue post-current for a period of time that is related to current duration. Tingling may be felt near the electrodes. There is some evidence that tDCS improves verbal fluency, word recall, and manual weakness in stroke cases. Anodal stimulation over the dorsolateral prefrontal cortex (20 minutes/day over 5 days) improved depression in one RCT. (Fregni ea, 2006) Further research is required.

Vagus nerve stimulation (VNS)

Vagal nerve³⁴⁵¹ stimulation (VNS), approved in the US for refractory partial-onset epilepsy and long-term management of treatment-resistant severe depression, is undergoing trials for refractory depression, bipolar cases (including rapid-cycling: Marangell ea, 2008), anxiety, bulimia, migraine and Alzheimer's disease. (Shuchman, 2007) As used for epilepsy, VNS is delivered with a device surgically implanted in the

that evidence for efficacy was growing. rTMS did not alleviate treatment-resistant OCD in a study involving daily left dorsolateral prefrontal cortex (over 10 sessions) stimulation. (Sachdev ea, 2007) Reductions in YBOCS scores may be related to relief of depression.

³⁴⁵¹ Vagal sensory afferent cell bodies in nodose ganglion send data to nucleus tractus solitarius. The latter sends information via ascending projections to forebrain (via parabrachial nucleus and locus coeruleus – these connect with many areas involved in mood modulation). It was noted early on that VNS given for epilepsy affected mood.

chest³⁴⁵² which delivers electrical impulses to the limbic system via the vagus nerve in doses of 0-3 mA for 30 seconds every 5 minutes. Neurologists noted that their patients felt better independent of improvement in seizures. (Mann, 2001) VNS changes blood flow in frontal, cingulate and thalamic areas. VNS seems to increase noradrenergic, serotonergic, and dopaminergic neurotransmission. Onset of action is slow and the therapeutic effect increases over time. There is evidence, albeit 'uncertain', (Patra & Coffey, 2008, p. 503) from open trials for its efficacy. (Rush ea, 2000; Corcoran ea, 2006) More rigorously conducted research is awaited, (Matthews & Eljamel, 2003b) and more needs to be learned about side-effects like vocal cord palsies. Because antidepressant effects tend to accrue over weeks to months, the use of VNS for maintenance treatment of chronic depression may be more fruitful than would its use as an acute measure. (Patra & Coffey, 2008, p. 503)

VNS is not a contraindication to ECT. (Sharma ea, 2009)

Deep brain stimulation (DBS)

Low voltage electrical stimulation of target areas³⁴⁵³ via stereotactically placed electrodes³⁴⁵⁴ is used to modulate transmission in specified cerebral pathways. It has been used for movement disorders (e.g. essential tremor; Bilateral globus pallidus DBS (Damier ea, 2007) and DBS and bilateral posteroventral pallidotomy have produced useful results in severe tardive dyskinesia: Mattay and Casey, 2003, p. 567), Parkinson's disease (DBS of subthalamic nucleus has been used since the 1980s), pain syndromes, and epilepsy. DBS in the anterior limb of internal capsule offers a possible new way of treating refractory OCD (Nuttin ea, 1999: anterior limbs of internal capsules; ventral caudate nucleus) and depression (subgenual cingulate gyrus; ventral caudate nucleus). The mechanism of action is not known but might be related to enhanced activity of GABA. Potential adverse effects include intracerebral haemorrhage, peri-operative confusion, both related to surgery. During stimulation there may be problems with speech or eye movement, paraesthesia, and muscular contractions.

Sleep deprivation (wake therapy)

Both TCAs and MAOIs suppress REM sleep. Early research suggested that depressives did not improve if they failed to experience significant REM rebound. Depressives may improve with sleep deprivation. Deprivation of REM sleep³⁴⁵⁵ leading to alleviation of depression was reported in the late 1960s. If an animal was awakened before each episode of paradoxical sleep it began to show increased activity in all areas. Some reports suggested that total sleep deprivation could produce improvement in 'endogenous' depression. The duration of relief from depression varied. A faster response to clomipramine was found if the patient was deprived of sleep for one night before starting the drug.

During the late 1960s it was theorised that REM sleep was primed by metabolites of 5-HT and was triggered by ACh and noradrenaline. It is possible that sleep deprivation might work by increasing brain 5-HT. Clomipramine blocks 5-HT re-uptake into the presynaptic neurone. However, this is not a major function of many effective antidepressants.

Tests have shown that extroverts show greater amount of rebound after REM deprivation than do introverts. One of the major problems with attempts to treat mood disorders with sleep manipulation is the transient effect of any of the approaches employed to date. Also, staying awake requires motivation.

Psychosurgery/Neurosurgery

Reports of improvement in mental state date back to at least medieval times. Phineas Gage (1848) was respected railway foreman. Unfortunately, he had a crowbar driven through his frontal lobes. After this he became careless, uninhibited and unemployable. Ferrier, in his 1875 Croonian Lecture, reported that the removal of a large part of a monkey's frontal lobes led to tameness and docility with no sensorimotor deficits. In 1935 Fulton and Jacobsen reported that frontal lobectomy had a tranquillising effect in primates suffering from behavioural disorders due to an 'experimental neurosis'. In 1936 Moniz started to study ways in which

³⁴⁵² A small stimulus generator is placed beneath the clavicle and a lead from this is wrapped around the **left** vagus in the neck (the right nerve is avoided because it gives parasympathetic branches to the heart). The generator is programmed to deliver a fixed duration of stimulation, say 0.5 minutes every 5 minutes. The patient may cough or be hoarse during stimulation.

³⁴⁵³ E.g. the subgenual cingulate area (Brodman's area 25).

³⁴⁵⁴ Electrodes are connected to a battery or stimulator in the chest wall.

³⁴⁵⁵ Keep patient awake during second half of normal sleep span.

interruption of certain brain pathways (thalamo-frontal) could be used to control abnormal behaviour. Freeman³⁴⁵⁶ and Watts, a neurologist and neurosurgeon respectively, and others were responsible for refinements in technique. Modern stereotactic psychosurgery, such as Yttrium seed implantation, has two main aims: relief of severe, continuous or recurrent mental anguish due to psychiatric illness, and reduction of abnormal aggressiveness (as with amygdalectomy). The main indication in the past for psychosurgery was for intractable schizophrenia, but these people did least well, although schizoaffective disorder may be improved. The best results were achieved in depression with associated anxiety or in obsessional states. There is a 1-2% chance of one or more fits after the operation. The commonest procedure performed in Britain³⁴⁵⁷ was stereotactic subcaudate tractotomy.(Poynton ea, 1995) and was the only such intervention performed at the Geoffrey Knight Unit in London by the mid-1990s, with a total of 1,300 operations performed since 1961 (Freeman [1997] cites 501 operations between 1979 and 1995). Less commonly performed is limbic leucotomy and bilateral lesions in the cingulum bundle. (See Dougherty ea, 2002 for cingulotomy in OCD: a third or more of patients nonresponsive to medication and behavioural treatments showed at least partial improvement at a mean of 32 months.) The commonest reasons for stereotactic subcaudate tractotomy according to a 1993 report were major depression (75%), bipolar disorder (15%), OCD (3%), and others (7%). In bipolar cases, episodes of mania may be better controlled than episodes of depression. Antisocial personality traits, drug and alcohol abuse, and absence of informed consent are contraindications. Significant changes in symptoms may occur over a six-month period following surgery, and such changes may have some predictive value. Poynton ea (1995) found no lasting effect of stereotactic subcaudate tractotomy on neuropsychological function during their prospective follow up of 23 patients, despite some initial minor decrement in cognitive abilities. Suicide risk may be reduced by psychosurgery but it is not completely eliminated. The zero suicide rate reported after capsulotomy by Fenton (1999) may relate to its more common use in OCD than in depression. Follow up of capsulotomy (for refractory anxiety) patients by Rück ea (2003) in Sweden revealed a significant amount of apathy and impaired executive function. A non-controlled long-term follow-up (mean 10.9 years post-surgery) of 25 consecutive OCD cases (Rück ea, 2008) found that capsulotomy is effective, has a substantial risk of adverse effects (weight gain, executive dysfunction, apathy, or disinhibition), that smaller lesions are safer, and that high radiation doses and multiple procedures should be avoided. Psychosurgery has been outlawed in a number of European countries and in 1996 Norway offered compensation to patients who had undergone such surgery in the past. Before considering a patient for psychosurgery he must have been suffering for a long time and all other appropriate treatments should have been given an adequate trial. Modern drug and behavioural treatments have drastically reduced the need for surgery. The use of psychosurgery is strictly regulated under British legislation and under the Irish Mental Health Act, 2001: psychosurgery requires written consent from the patient and authorisation from a Tribunal. Follow-up research must be of high quality.(Matthews & Eljamel, 2003a)

The use of the gamma knife (focused gamma rays), with no need to open the skull, may make psychosurgery more acceptable in the future. Psychosurgery remains a highly controversial intervention.(Persaud ea, 2003)

Insulin therapy

Manfred Sakel's famous 'coma treatment' for schizophrenia is now part of history, although it still has its advocates among those who used it (John Dunne, 1984, personal communication). Following the use of insulin to calm patients experiencing abstinence symptoms from opiates Sakel discovered that schizophrenics also benefited. Following an overnight fast an injection of insulin was used in the morning to cause coma. A couple of hours later glucose (NG or IV) was given to bring the patient out of coma. Some patients actually convulsed. Modified (non-coma) therapy with insulin has been tried for anorexia nervosa. Insulin coma therapy was shown not to be any better than barbiturate narcosis (Ackner ea, 1957) but it did not immediately go out of fashion.(Berrios, 2008, p. 27) The advent of neuroleptics offered a superior alternative. Nurses who were involved in 'coma therapy' tell us that vomiting was common and that the floors were often covered in a sugary solution.

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³⁴⁵⁷ Procedures used in the US include anterior cingulotomy, limbic leucotomy (anterior cingulotomy plus subcaudate tractotomy), and anterior capsulotomy (often using a gamma knife).

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Lithium and related treatments³⁴⁵⁸

Brian O'Shea

'The most important predictor of response to lithium is patient compliance'.(Shelley, 1995)

Lithium³⁴⁵⁹

Lithium³⁴⁶⁰

Does not occur freely in nature

The alkali metal³⁴⁶¹ has atomic weight of 3 (following hydrogen and helium) - it is always combined and is most often found in igneous rocks³⁴⁶²

Outer electron, unlike the two inner electrons, is easily displaced, hence, Li+ Lithium salts common in environment

Has no known function in human body, which normally contains about 0.1% of therapeutic level of lithium

Found in all body fluids, including saliva and semen

Side effects determined by peak level

Therapeutic effects relate to 12-hour level

Blood level should be taken before morning dose is taken (if the patient is on such a schedule)

Is quickly absorbed

Peak serum levels reached 1-2 hours after ingestion

Half-life is 14-30 hours

No protein binding

The lithium ion-selective analyser gives lithium level within 1 minute (whole blood)

Send³⁴⁶³ 5-10 ml clotted blood in plain tube, from which serum can be separated

Do not send anticoagulated blood³⁴⁶⁴

³⁴⁵⁸ O'Shea,(1993) reviewing pharmacological alternatives to lithium (Gk. *lithion*, stone) in bipolar affective disorder, found drugs more effective in preventing manic than depressive episodes. The commonest single drug implicated in British negligence claims is lithium: failure to appreciate the dangers of dehydration and concurrent use of diuretics, failure to monitor thyroid and kidneys, and poor communication between the laboratory and the clinician over serum lithium results.(Bradley, 1997) Lithium monitoring falls below guidelines in Ireland.(Udumaga & Mannion, 2010) Although there were isolated applications of lithium for affective disorders during the 19th century,(Schou, 1992) John Cade, who used lithium during the 1940s to treat mania in Australia and found it to be effective, is acknowledged as being responsible for its introduction to psychiatry. Patients relapsed when the lithium was stopped. Cade noticed that lithium had a slowing effect on animals. Before this, lithium had been tried in epilepsy (the bromide salt), gout, and, with disastrous results, as the sodium salt as a substitute in heart patients.

³⁴⁵⁹ Arfwedson and Berzelius discovered lithium sulfate in petalite in 1817, and elemental lithium was isolated in the mid-nineteenth century.

³⁴⁶⁰ Atomic number 3, atomic weight 6.94, 3 protons, 3 electrons, 4 neutrons.

³⁴⁶¹ Other alkali metals include sodium and magnesium.

³⁴⁶² Major sources of lithium include spodumene (up to 8% lithium oxide), brines (e.g. Great Salt Lake, Utah), amblygonite (up to 10% as complex phosphate), mineral spring waters (e.g. Perrier), lepidolite, and petalite.

³⁴⁶³ Lithium concentration can be measured by flame emission photometry or atomic absorption spectrophotometry. Ideally, serum should be separated as quickly as possible, preferably within an hour since lithium moves into erythrocytes after that time.

The kidney excretes lithium in favour of sodium, which it retains. A small amount of lithium appears in saliva and the use of saliva as a substitute for serum when estimating levels has been attempted. Red blood cell levels are a better reflection of intraneuronal levels and white blood cell levels may be better still. Brain lithium levels are typically about half those in serum. There appears to be little difference in the mean serum concentration-time plot between the available lithium preparations e.g. Camcolit and Priadel. Priadel liquid³⁴⁶⁵ is sugar-free. Phasal is another example of a lithium carbonate preparation.

Early studies suggested that patients with serum levels of 0.8-1.0 mmol/L have only a 13% relapse rate but experience side effects³⁴⁶⁶, whereas patients with serum levels of 0.4-0.6 mmol/L have a 28% relapse rate and much less of side effects. Older, higher suggested lithium serum level ranges tend to linger on in laboratory reports. Such levels are more suited to treatment of mania (with frequent measurements) than prophylaxis (with less frequent monitoring). Some, perhaps 28% (Marangell *et al.*, 2003, p. 1108), lithium-treated patients complain of memory impairment (e.g. forgetting a friend's name). Others complain of slowed reaction time and the feeling that life is now less colourful and interesting. These may respond to a lowering of the dose of lithium. Objective testing of memory is generally normal and some patients seem to miss their manic episodes. Lithium taken during ECT is thought to contribute to confusion, although this has not been a significant problem in this author's experience. Lithium can cause coarsening or partial loss of hair. Mild mood fluctuations are generally a warning not to stop lithium.

The recommended therapeutic lithium serum levels are the same for both adults and children.(Dulcan, 1996)

Key lithium studies summarised, including outcome

1979. Healthy volunteers on lithium show a small but consistent decrease in the ability to learn, concentrate and memorise.

1983. MRI (NMR) reveals longer proton T1 relaxation times in brain tissues of bipolar depressives, normalising with lithium therapy (similar results reported in red blood cells 3 years later).

1984. NIMH collaborative trial finds only one-third of patients remains well on lithium over 2-year period.

1989. Protein kinase C activation is blocked by lithium. Since protein kinase C (which potentiates neurotransmitter release) activation also potentiates 5-HT and noradrenaline release, this effect of lithium may be important in the treatment of mania and the prophylaxis of bipolar affective disorder.

1990. Response to lithium prophylaxis may depend on past course of bipolar affective disorder, e.g. better for sequence mania-depression-free interval than for depression-mania-free interval and rapid cycling with continuous circling course.

1991. 40% of bipolars had good outcome, 41% had fair outcome, and 19% had poor outcome. Poor outcome associated with frequent pre-lithium admissions, negative family affective style, lower social class, and current alcohol/substance abuse.

³⁴⁶⁴ Lithium heparin could be the anticoagulant and give false results.

³⁴⁶⁵ 520 mg lithium citrate/5 ml = 200 mg lithium carbonate. The citrate may cause less nausea and vomiting than the carbonate.

³⁴⁶⁶ Tremor, diarrhoea, urinary frequency, weight gain, and a metallic taste in the mouth.

Mania preceding depression predicts a better response to lithium than depression preceding mania.

1992. Lithium does not have an extreme mood normalising effect in well-controlled bipolar affective disorder patients i.e. normal moods remain.

Lithium may reduce suicidal behaviour even when it does not appear to control mood disorder.

Neurotoxicity at normal therapeutic levels is more likely if there are organic cerebral problems (incl. abnormal EEG), rapid dosage changes, or 'genetic susceptibility'.

1993. 26 cases of lithium-induced hyperparathyroidism³⁴⁶⁷ found in the literature – a reversible disorder.

1994. The chief reason for the difference between the efficacy of lithium prophylaxis in studies and its effectiveness in clinical practice is poor compliance in the latter context.

1995. Excess mortality in affective disorders is due to suicide and cardiovascular disease and lithium may reduce the likelihood of such events.

Relative risk of death among patients with mood or schizoaffective disorders is 1.7 times higher when off lithium compared to being on lithium; relative risk of suicide is 4.8 times higher if off lithium compared to that when on lithium.

1996. Improved psychosocial functioning for bipolar I patients on lithium above and beyond effects of relapse prevention v those not on lithium.

1998. High dropout rate among bipolars followed up after 5 years on lithium. Those on lithium had a lower hospitalisation rate but may be a self-selected group.

Poorer response to lithium with mixed episode, dysphoric mania, rapid cycling, many previous episodes, impaired functioning between episodes, and a depression-mania-euthymia course.

2000. Baldessarini and Tondo, looking at stability of response over 30 years, find that lithium benefits were not exaggerated in the past; nor has lithium lost efficacy. Poor results may be due to accumulation over time of complex, less treatment-responsive illnesses.

2001. Lithium monotherapy is as effective as lithium plus imipramine or paroxetine in bipolar depression; lithium levels below 0.8 mEq/L have a lower response rate than have lithium plus an antidepressant.

2003. Risperidone superior to placebo used in combination with lithium or divalproex in acute mania.

2004. Adding olanzapine to lithium or valproate for acute dysphoric mania improved depression, mania and suicidality.

2005. Danish study found that lithium reduces risk of suicide.

Lithium effective in preventing suicide, deliberate self-harm, and death from all causes in mood disordered patients (systematic review)

Divalproex was not more effective than lithium in longterm management of rapid-cycling bipolar disorder.

Young and Hammond (2007) point out that lithium use may be waning despite increasing knowledge about this efficacious tool. The key mechanism of therapeutic action is not known for sure. (Jope, 1999) Lithium is thought to increase presynaptic destruction of catecholamines, inhibit neurotransmitter release, decrease sensitivity of postsynaptic receptors, affect transfer of sodium and calcium and therefore affect both the release of neurotransmitters and the activity of receptor sites, cause sodium to be pumped out of the cell in depression (and possibly into the cell in mania), inhibit prostaglandin E³⁴⁶⁸, increase insulin release³⁴⁶⁹, increase permeability of membranes to magnesium and calcium, and cause EEG changes such as reduction in REM sleep duration. The

³⁴⁶⁷ Lithium reduces sensitivity of calcium-sensing receptor.

³⁴⁶⁸ Which is stimulated by cyclic adenosine monophosphate (cAMP).

³⁴⁶⁹ A possible reason for increased weight: glycogen formation in muscle.

corticosteroid rhythm is restored either as a direct affect of lithium or as a result of the effect on activity. Lithium moves out of cells more slowly than sodium. When receptors are affected by neurotransmitters there is then an effect on second messenger systems beneath the cell membrane. Effects on one of the latter systems, the phosphoinositide system, may explain the actions of lithium.(see box) Perhaps the ultimate effect is to attenuate protein kinase activity since a reduction in protein kinase C (PKC) levels parallels the time course for lithium's delayed onset of action. Both adenylate cyclase and phosphoinositol metabolism affect PKC levels which are known to facilitate release of a wide range of neurotransmitters. Valproate and carbamazepine also decrease PKC activity. In clinical doses, carbamazepine decreases cAMP production and CREB phosphorylation.(Chen ea, 1996)

Lithium – possible mechanisms producing therapeutic actions

Antimanic action – moderate attenuation of DA function, increased GABA neurotransmission, increases in or stabilisation of Ach function.

Arachidonic acid (an n-6 polyunsaturated fatty acid) and its metabolites (incl. eicosanoids and anandamide) are important second messengers that are able to modulate ion channels, neurotransmitter uptake, synaptic transmission, apoptosis, and so on. Rat studies show that lithium and anticonvulsant drugs decrease arachidonic acid turnover.

Drugs targeting enzymes involved in the arachidonic acid cascade might therefore be beneficial in mania, e.g. cyclooxygenase 2 inhibitors. Competition between arachidonic and docosahexaenoic acid that occurs in the body suggests that docosahexaenoic acid or its precursors might also be useful therapeutic agents.(Rapoport & Bosetti, 2002)

Many authorities suggest that lithium therapy for acute mania should not be considered to have failed unless plasma levels of 1.2-1.5 mEq/L have been reached and maintained for two weeks.

Antidepressant action – increased synthesis and turnover of presynaptic 5-HT (including increased tryptophan uptake), increased 5-HT release and reduced binding of function of 5-HT₂ receptors (especially hippocampal), increased responses mediated by postsynaptic 5-HT_{1A} receptors, increased metabolite of 5-HT in CSF, increased platelet 5-HT uptake, increased neuroendocrine responses to 5-HT agonists, reduced beta-adrenoreceptor-mediated stimulation of adenylate cyclase, and a tendency to downregulate alpha-2-adrenoreceptor function.

All of the above effects are modest, some have been found in animals, and some actions have been demonstrated in humans. It is likely that effects on second messengers and signal transduction systems are crucial. Lithium inhibits neurotransmitter-receptor-coupled adenylate cyclase activity and cyclic AMP formation *in vitro*. Lithium inhibits coupling of neurotransmitter receptors to G proteins, which inhibits G protein activation of adenylate cyclase. Lithium also inhibits the other major second messenger system, which involves phosphoinositide metabolism. Lithium may alter neuronal function via effects on ion distribution and kinetics.

Neural plasticity – lithium may affect this by actions on glycogen synthetase kinase-3 β ³⁴⁷⁰ (GSK 3 β), cyclic AMP-dependent kinase, and protein kinase C.

High doses required in the acute treatment of mania. The treatment needs to be monitored closely.(Kehoe & Mander, 1992) Treatment classically takes 7-10 days to have effect. Antipsychotic drugs bring behaviour under control quicker than lithium.

³⁴⁷⁰ Lithium has a tendency to elongate circadian periods and cause a phase delay of circadian rhythms and it prolongs the therapeutic effect of total sleep deprivation in depression. Inhibition of GSK 3 β , which modifies parts of the molecular clock, may account for lithium's actions in this regard.

Research in the 1970s on the lithium prophylaxis of bipolar disorder found a relapse rate of 23% on lithium compared to 68% with placebo, and 75% of relapses in lithium-prescribed patients were ascribed to non-compliance. Other possible uses include prophylaxis of schizoaffective disorder and some more doubtful applications. However, dipsomaniacs may respond, probably because of an affective underpinning. Lithium is not an antidepressant *per se* although its addition may³⁴⁷¹ augment antidepressant drug effects, and a lithium-imipramine combination may have superior prophylactic value in unipolar depression than either drug alone. Lithium reduces the intensity and duration of mood swings and full effect may require 6-24 months. Two manic episodes or one manic and two depressive episodes seem a reasonable guideline, although the length of time between episodes and the social consequences of attacks are equally important.³⁴⁷²

Sometimes one attack of mania is enough reason for prophylaxis. (Birch ea, 1993) The patient's co-operation is all-important. Patient reliability is important. Family planning advice and a booklet outlining the basic facts of lithium therapy and its side and toxic effects are other important considerations.

Tests prior to commencement and at intervals during treatment include physical examination, serum creatinine, basic haematological work-up, thyroid function tests (especially TSH) and (if indicated, especially if patient > 50) an ECG. Serum lithium levels are usually tested weekly for 3-4 weeks and 3-monthly thereafter, and thyroid and renal functioning are tested twice a year over the long term, or more often if indicated. Lithium should not be stopped in cases of relapse of bipolar or unipolar affective disorder. The episode should be treated along orthodox lines³⁴⁷³.

Withdrawal of lithium, especially sudden withdrawal, is associated with a high relapse rate, increased number of inpatient days, increased doses of antipsychotic drugs, and, according to some but not all researchers, a withdrawal syndrome. Some patients may simply become irritable and emotionally labile on abrupt withdrawal from lithium. Post ea (1992) contended that if effective lithium prophylaxis is stopped it may not work a second time although this argument is not convincing.

Page ea (1987) investigated the fate of unipolar and bipolar affective disorder patients most of whom had taken lithium for at least 13 years. At follow-up 49% experienced a complete remission, 41% had a partial but significant response and 10% had no response to lithium. No specific individual or illness factor was found to correlate with a favourable outcome, and no correlation was discovered between the average serum lithium level and outcome. In a retrospective study of manic patients, Golney and Spence (1986) found a favourable response to be associated with bipolar status with a family history of depression or mania, unipolar status with endogenous illness, and with the absence of significant disturbance of personality. In the same study the response to lithium over 6 months in unipolar illness and over the first year in bipolar illness was strongly associated with long-term response. According to Prien and Gelenberg (1989), the average failure rate for lithium in preventive treatment studies was 33%, where a failure was defined as episodes needing admission or the addition of other drugs. Only one-fifth of patients suitable for lithium could expect no recurrences.

Lithium, usually combined with antidepressants, has been used successfully in the treatment of deluded depressives who refuse ECT, although a combination of antidepressant and antipsychotic drugs is favoured.

Lithium therapy may reduce the frequency of repeated aggression or self-mutilation in the mentally handicapped, psychotics, or delinquent subjects. One possible mechanism is that it may elevate 5-HT levels. There are no special features in such cases that would help one to predict a useful response.

Lithium causes a reversible nephrogenic diabetes insipidus with polyuria³⁴⁷⁴, especially with high serum levels. Polyuria is produced by inhibition of cAMP-dependent action of

³⁴⁷¹ Not all studies concur.

³⁴⁷² The present author has no rigid preconceptions about when to start lithium prophylaxis.

³⁴⁷³ With lithium dosage changes, ECT, antidepressants, or antipsychotics, etc.

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ADH on distal tubules and collecting ducts. Amiloride reduces lithium-induced polyuria without affecting lithium or potassium levels. This potassium-sparing diuretic increases ADH by blocking lithium entry to ADH-sensitive cells. (Martin, 1993) Amiloride 10-20 mg/day reduces lithium requirements, so check lithium levels more frequently. Adding hydrochlorothiazide (50 mg/day) to amiloride increases the risk of toxicity. Indometacin (indomethacin), 50 mg TID is only used when immediate normalisation of polyuria is required, and then only as a short course. It inhibits cyclo-oxygenase and prostaglandin synthesis. Other possible interventions include dose reduction, single daily dosing (though assists renal recovery), and potassium supplements.

Depending on individual circumstances the present author usually starts patients on an average dose of 800 mg lithium carbonate at night, further dose changes being dictated by clinical state and serum levels. Short-acting preparations may cause nausea, whereas delayed-release preparations may be more likely to induce diarrhoea. The difference between the two preparations remains controversial³⁴⁷⁵.

Amdisen and Schou³⁴⁷⁶ of Denmark originally suggested serum levels (taken 12 hours after last dose) of 0.8-1.2 mmol/L. Hullin of Leeds has shown that lower levels are effective but high relapse rates occur below 0.4 mmol/L. The present author employs the range 0.6-0.9 mmol/L. (even lower in the elderly). Prophylaxis, this author believes, is generally for life.

Some factors increasing the likelihood of lithium intoxication

Overdose

High prescribed dose

Renal disease

Excess sweating

Dehydration

Hyponatraemia

Vomiting

Diarrhoea³⁴⁷⁷

Tropical heat

Sauna

Infection

Fever

Trauma/surgery³⁴⁷⁸

Diuretics³⁴⁷⁹

Indomethacin

Tetracyclines³⁴⁸⁰

³⁴⁷⁴ The patient should drink non-sweet fluids to compensate.

³⁴⁷⁵ The most important thing in practice is to avoid intoxication.

³⁴⁷⁶ Mogens Schou (b. 1918), son of psychiatrist and manic-depressive H. J. Schou.

³⁴⁷⁷ An SSRI added to lithium increases burden of diarrhoea.

³⁴⁷⁸ Stop lithium 1-2 days preoperatively, give IV fluids during surgery, and re-start lithium when oral fluids tolerated.

³⁴⁷⁹ Especially sodium-losing diuretics such as thiazides. Potassium-sparing and loop diuretics are relatively less likely to raise lithium levels.

³⁴⁸⁰ These usually only slightly increase lithium levels.

Digoxin
Alpha-methyldopa ³⁴⁸¹
Phenylbutazone
Muscle relaxants ³⁴⁸²
Cyclooxygenase-2 (APA, p. 583)
Pregnancy
Excess alcohol intake ³⁴⁸³
Drastic slimming

The combination of lithium, a thiazide diuretic and digoxin can cause digoxin toxicity via induction of hypokalaemia. If a diuretic is necessary then a loop diuretic such as frusemide may be used. When treating a hypertensive patient who is taking lithium, consider a beta-blocker or clonidine, but avoid thiazide diuretics. Diclofenac, indomethacin, metronidazole, spectinomycin, ibuprofen and piroxicam have been reported to raise the plasma lithium concentration. Renal prostaglandins, especially PGE₂, are strong vasodilators of the renal circulation. NSAIDs may inhibit prostaglandin synthesis and lead to lithium intoxication via ischaemia³⁴⁸⁴. Renal function is most likely to be adversely affected by NSAIDs if it is already compromised, and prostaglandins become progressively more active with a deterioration in kidney function.

Some factors that give a falsely low lithium concentration in tissues include >13 hours since last dose ingested³⁴⁸⁵, brain damage, and phenytoin. AIDS patients are at increased risk of lithium toxicity, even with therapeutic serum levels.³⁴⁸⁶

Lithium intoxication usually develops over days or more quickly in the case of overdose. Lithium should be stopped for a few days during an intercurrent illness or suspected toxicity. Lithium intoxication has to be a clinical diagnosis because it results from high intracellular lithium concentrations, which may not be reflected in serum levels.

Features of intoxication

Sluggishness, drowsiness, dysarthria
 Anorexia, diarrhoea, vomiting
 Vertigo, coarse tremor, agitation, restlessness, hypertonia, hyperreflexia
 Widespread shakes, muscle fasciculation, convulsions, transient hemiparesis
 Irregular breathing, coma
 ECG changes (flat or inverted T wave³⁴⁸⁷, U waves, and conduction delays, e.g. first degree heart block).

Intoxication may lead to full recovery, death, persistent renal symptoms, spasticity, cognitive impairment, or permanent cerebellar damage with loss of Purkinje cells. Polyneuropathy may require weeks or months to resolve. Lithium intoxication (even with therapeutic levels) can produce myoclonus and EEG changes resembling those found in

³⁴⁸¹ This can cause intoxication even with therapeutic lithium serum levels.

³⁴⁸² Succinylcholine and pancuronium are potentiated by lithium and may occasionally lead to prolonged apnoea.

³⁴⁸³ Leading to loss of salt and water.

³⁴⁸⁴ Aspirin, paracetamol, and sulindac (Clinoril) appear to be safe with lithium.

³⁴⁸⁵ Because of the slope in the graph, a sample taken after 12 hours is a better reflection of the 12-hour level than one taken before 12 hours.

³⁴⁸⁶ This may be due to damage to the blood-brain barrier.

³⁴⁸⁷ 50% of lithium-treated patients have benign/reversible T wave flattening.

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CJD, but these are reversible.³⁴⁸⁸ Management of intoxication includes early diagnosis and treatment of overdose (initially stomach washout and activated charcoal left in stomach³⁴⁸⁹). In the usual case one can give oral or IV NaCl, Na₂SO₄, or MgSO₄³⁴⁹⁰, osmotic diuresis with acetazolamide (Diamox) or urea³⁴⁹¹, or renal dialysis. A rebound rise in lithium levels may follow haemodialysis. Neurological recovery may lag behind decreases in serum lithium levels. This is explained by the relatively slow equilibration between intracellular (incl. neuronal) and plasma concentrations. Dialysis patients do not eliminate Li⁺ naturally. Because lithium is readily dialyzable (and not excreted by kidneys in dialysis patients - it is only removed at dialysis), it is therefore given (300-600 mg lithium) to patients - orally or into dialysate - on renal dialysis who need lithium for their affective disorder *after* their dialysis sessions. Daily dosing is not required. Serum levels are measured some 3-4 hours after dialysis because serum levels may rise following dialysis due to equilibration with the tissues.

Contraindications to lithium therapy (vary with circumstances)

Patient unreliability
Early pregnancy³⁴⁹²
Elective surgery
Uncompensated renal disease
Severe cardiac disease³⁴⁹³
Diuretic therapy

Lithium may cause acute tubular necrosis.

The classic foetal anomaly reported with lithium is Ebstein's anomaly³⁴⁹⁴. The cardinal feature is the displaced tricuspid valve. Lithium should not be given to patients with myasthenia gravis³⁴⁹⁵, Addison's disease or untreated hypothyroidism.

Renal damage is most likely with intoxication. (Hetmar ea, 1991) Nephrotoxicity may relate more to the duration of exposure to peak lithium levels than to the absolute level of any peak, suggesting that once-daily dosing is the ideal prescription. Glomerular sclerosis, tubular atrophy, and interstitial fibrosis may occur in lithium treated patients and animals. However there is some evidence that the incidence is not particularly high when function is considered³⁴⁹⁶. Many authors have commented on the non-likelihood of death from lithium-induced nephropathy. Lithium can be used during maintenance haemodialysis where it has been given after dialysis in doses of 300-600 mg/day. Lithium-treated patients require more AVP (ADH) to maintain urine of a given osmolality than do non-lithium-treated cases. Some increase in serum creatinine concentrations and a lowering of maximum concentration capacity in lithium-treated patients over time is neither uncommon nor worrying. GFR may be normal in 85% or mildly decreased in patients on lithium. Serum creatinine may be normal in the elderly despite impaired renal function because of reduced muscle mass. The most prevalent renal effect of lithium is an impaired concentrating ability.

Estimated glomerular filtration rate (eGFR) (Morriss & Benjamin, 2008)
Calculated as:

³⁴⁸⁸ Lithium does not exacerbate epilepsy except for the induction of myoclonus during lithium intoxication.

³⁴⁸⁹ In fact, little lithium is absorbed from the stomach and there is a risk of worsening electrolyte imbalance.

³⁴⁹⁰ Cations exchanged for Li⁺ in the renal tubules.

³⁴⁹¹ Carbimide.

³⁴⁹² At parturition there is a diuresis with risk of intoxication, so reduce dose of lithium to prevent this.

³⁴⁹³ Unstable congestive cardiac failure or sick sinus syndrome. A recent myocardial infarction is a relative contraindication because of the risk of arrhythmias.

³⁴⁹⁴ Described by Wilhelm Ebstein in 1866.

³⁴⁹⁵ Because of blockade of Ach release and potentiation of neuromuscular blocking agents like succinyl choline.

³⁴⁹⁶ 5-10% of patients on long-term lithium experience impaired tubular function.

GFR = 175 x [seum creatinine (µmol/L)^{-1.154} x [age^{1-0.203} x [1.212 if Black] x [0.742 if female], ml/min/1.73 m²

eGFR is more sensitive indicator of stage 3 chronic (asymptomatic) renal disease³⁴⁹⁷

A single eGFR estimation is not a reliable estimation of stage 3 chronic (asymptomatic) renal disease

May be inaccurate if patient > 70 or < 18 years, pregnant, has an amputation, is malnourished/dehydrated, or of Afro-Caribbean origin

Falls, muscle injury, or injections can increase eGFR

Lithium can be given to renal transplant cases if frequent serum level monitoring is carried out. Cyclosporine can increase lithium serum levels by decreasing its excretion, thus necessitating a lowering of the lithium dosage. Live donor kidneys handle lithium better than cadaver kidneys.

Lithium interferes adversely with the iodination and release of thyroid hormones. It may interfere with their actions on target tissues in the same way that it reduces renal sensitivity to arginine vasopressin (AVP/ADH). After a few years on lithium some authors have found a 3-50% incidence³⁴⁹⁸ of goitre (larger size on ultrasound in smokers) and 4-21% incidence of hypothyroidism³⁴⁹⁹. Goitre appears to be more common the longer the patient is taking lithium. Pre-existing anti-thyroid antibodies or a family history of thyroid disease increase the chances of developing lithium-related hypothyroidism. Hypothyroidism and euthyroid goitre are managed with thyroxine supplementation³⁵⁰⁰ and the continued administration of lithium. Many therapists now give thyroid hormone supplementation for persistently raised TSH, even if T4 levels are normal. (Owens, 2004, p. 291) Thyroid function normalises in a couple of months when lithium is stopped. Whether uncommon cases of hyperthyroidism can be attributed to lithium is difficult to say. Rosser (1976) described the emergence of thyrotoxicosis after lithium was stopped and Byrne and Delaney (1993) reported a case where thyroid ophthalmopathy regressed after stopping lithium.

A raised leucocyte count may occur in people on lithium. The mechanism appears to be stimulation of granulocyte-stimulating factor and interleukin-6. It seems to be harmless and reverses soon after stopping lithium. It is suggested that lithium be withheld on chemotherapy days or during cranial (but not other) radiation in cancer patients. (Fawzy & Greenberg, 1999)

Exacerbation of psoriasis is common.³⁵⁰¹

Side effects include polyuria, thirst, nausea (take after food), loose stools, metallic taste, fine tremor, weight gain³⁵⁰², Parkinsonism³⁵⁰³, fatigue, and delayed reaction time whilst driving³⁵⁰⁴. Side effects may be more common in those patients who have EEG abnormalities. Rarely patients complain of itchy or burning eyes or blurred vision.

Pooled data from a number of studies (Goodwin & Jamison, 1990) found that the most frequent subjective complaints were (percentage of patients): thirst (36%), polyuria (30%), memory difficulties (28%), tremor (27%), increased weight (19%), drowsiness (12%), and diarrhoea (9%), with over one-quarter having no complaints. The most likely problems leading to non-adherence were memory difficulties, weight gain, tremor, polyuria, and drowsiness.

³⁴⁹⁷ Grade 3 is associated with a 40% increase in cardiovascular mortality.

³⁴⁹⁸ The higher figures may not reflect clinical reality.

³⁴⁹⁹ Increased TSH occurs much more often than clinical hypothyroidism.

³⁵⁰⁰ E.g. 50 µg Eltroxin to start.

³⁵⁰¹ A full list of **cutaneous adverse effects** is daunting: folliculitis, proliferation of viral warts, hair loss, toe nail dystrophy, exfoliative dermatitis, acneiform eruptions, LE-like syndrome, and psoriasis (worsening; increased resistance to treatment; and conversion to pustular type). (Edwards, 1995)

³⁵⁰² Mean of 4 Kg; affects 75% of patients.

³⁵⁰³ Disputed by Factor (2004, p. 223) who suggests that it may not occur in the absence of anticonvulsants.

³⁵⁰⁴ The latter may lead to accidents, esp. in the elderly. (Etminan et al., 2004)

Dyspepsia may improve by dividing the daily dose or by changing the proprietary preparation. Tremor may improve with smaller and more frequent doses, avoidance of caffeine³⁵⁰⁵, or the addition of beta-adrenoceptor blocking drugs³⁵⁰⁶. Primidone (Mysoline) can also be used for lithium-induced tremor.(Factor, 2004, p. 219) However, primidone has been associated with psychosis and depression.

Sudden cessation of caffeine intake can increase lithium blood levels by 24%.

Lithium can cause a golden discoloration of the distal nail plates. The combination of lithium and antipsychotic drug can lead to somnambulism, which should respond to dose reduction.

Cohen and Cohen caused a scare by reporting 4 cases of brain damage in subjects on both lithium and haloperidol, occurring in the one hospital, at the same time. When mania 'breaks',³⁵⁰⁷ heavy doses of these drugs cause EPS (extrapyramidal symptoms) which may be marked. If the patient is monitored closely and if doses are kept low it should be possible to prevent such problems. Cogwheel rigidity from lithium is unresponsive to anticholinergic drugs.

Lithium can potentiate the effects of muscle relaxants. It does not ordinarily change the effects of alcohol. Folate is considered necessary for 5-HT synthesis in the brain. A number of studies conducted during the 1980s found a slightly lower plasma folate concentration in lithium-treated patients. Copen ea(1986) found that giving a supplement of folic acid (300-400 micrograms/day) to patients on lithium caused those with the highest folate levels to show a significant reduction in affective morbidity.

Calcium blockers given with lithium can cause heart block and neurotoxicity. The chief culprit here is verapamil³⁵⁰⁸, whereas reports on diltiazem are less clear. Enalapril, an ACE inhibitor, can increase lithium levels to the toxic range. Verapamil can reduce lithium levels. Theophylline increases renal lithium excretion, thus lowering serum lithium levels.

Non-adherence with lithium therapy is associated with substance abuse and more admissions to hospital.

Non-response to lithium treatment in adherent patients is associated with female sex, young age, and a previously chronic illness course.

Other agents

Carbamazepine (e.g. Tegretol)

Carbamazepine, an iminodibenzyl and a relative of imipramine, is indicated for generalised tonic-clonic seizures, partial seizures, paroxysmal pain (e.g. trigeminal neuralgia), alcohol withdrawal, BZD withdrawal, mania, and prophylaxis of bipolar affective disorder³⁵⁰⁹. It may exacerbate petit mal (absence) seizures and is unlikely to be helpful in their management. According to Ballenger (1988), factors potentially predictive of antimanic response to carbamazepine include non-response to lithium, rapid or continuous cycling, more severe mania, depressed/anxious/dysphoric patient, more severely ill patient, schizoaffective disorder, evidence of organicity, primarily manic episodes, no family history, and early onset. According to Post ea (1997), an antidepressant response to carbamazepine might be associated with temporal hypermetabolism, but not the more typical frontal hypometabolism associated with depression.

Teratogenicity is not discussed. Carbamazepine should be avoided in those patients who have AV conduction defects³⁵¹⁰ or porphyria. The drug should be stopped if there is an

³⁵⁰⁵ Coffee, tea, cola, etc.

³⁵⁰⁶ E.g. propranolol 10-20 mg prn/bid/tid depending on circumstances.

³⁵⁰⁷ I.e. when the patient becomes euthymic.

³⁵⁰⁸ Bradycardia and movement disorders such as choreoathetosis may occur.

³⁵⁰⁹ And perhaps unipolar melancholic depression.(Stuppaeck ea, 1994) Young ea (2010, p. 632) consider carbamazepine to be a third-line prophylactic agent.

³⁵¹⁰ Anything greater than first degree heart block.(Brown ea, 2000)

allergic skin reaction or deterioration in liver function. Routine liver function tests may be performed more often for legal reasons rather than for cost-effectiveness; Dubovsky *et al.* (2003, p. 498) argues that hepatotoxicity, a rare phenomenon with anticonvulsants, may be picked up more readily by clinical examination than by laboratory examination. White cell counts and LFTs should be performed at baseline and, perhaps, at intervals thereafter. However, it has been argued that routine WCC counts will miss agranulocytosis because of its rarity and sudden onset. (Dubovsky *et al.*, 2003, p. 498; Marangell *et al.*, 2003, p. 1112) It is probably safer to tell the patient to report pyrexia, pharyngitis, other infection, petechiae, or weakness and pallor. (Marangell *et al.*, 2003, p. 1112) A non-progressive or fluctuating leucopaenia (and anaemia), often early in treatment, is common and usually harmless. However, should the leucopaenia be severe or be accompanied by clinical signs (e.g. pyrexia or sore throat) the drug should be stopped and the WCC checked. Post *et al.* (1997) estimated that serious side effects, such as agranulocytosis and aplastic anaemia, occur in only 1 in 10,000 to 120,000 treated patients³⁵¹¹. It may be necessary to cover sudden withdrawal with a BZD. Carbamazepine may interfere with driving and it can cause folate deficiency. The half-life of carbamazepine is 13-17 hours and there is 70-80% protein binding. Drugs such as cimetidine, dextropropoxyphene, diltiazem, erythromycin, INAH, viloxazine³⁵¹², and verapamil inhibit the metabolism of carbamazepine. Nifedipine (e.g. Nifed) does not have this effect. Fluoxetine may increase carbamazepine levels. Valproate raises the concentration of the toxic 10,11-epoxide metabolite of carbamazepine; therefore, whilst carbamazepine levels may be normal the patient may be toxic as the metabolite is not being measured. Carbamazepine induces liver enzymes and can reduce the effectiveness of certain drugs, e.g. antipsychotics, steroids (including oestrogen), theophylline, warfarin, and other antiepileptic drugs. TCA plasma levels may be reduced by 40-45% for the same reason. The dosage of anticoagulant drugs may need to be changed. Anovulant drugs may show reduced efficacy and there may be breakthrough bleeding or spotting; it is recommended that a pill containing at least 50 mcg of oestrogen is used or that another method of contraception is employed. It is not recommended that carbamazepine be given with or within 2 weeks of MAOI therapy because of the danger of a hypertensive crisis. This is because it is a tricyclic drug. However, the combination has been safely employed. (Ketter *et al.*, 1995) The side effects of carbamazepine, usually most marked early in treatment, are listed in the box. The usual recommended range for the prophylaxis of bipolar affective disorder is 4-12 mg carbamazepine/L plasma.

Side effects of carbamazepine

CNS – dizziness, diplopia, blurred vision, headache, somnolence, ataxia, confusion (with agitation in elderly), dystonia, worsening of multiple sclerosis symptoms
 GIT – dry mouth, nausea, diarrhoea, constipation, anorexia
 Metabolic – water intoxication, hyponatraemia
 Endocrine – low T4 level with normal TSH level³⁵¹³
 Skin – reversible generalised erythema in c 3%, and (rarely) severe reactions like exfoliative dermatitis, Stevens-Johnson syndrome (rash with symptoms equivalent to a severe burn – may kill from superimposed bacterial infection or lead to disfigurement), toxic epidermal necrolysis, hair loss

³⁵¹¹ Some authors put it at 1 in >575,000 treated patients/year.

³⁵¹² Withdrawn from market.

³⁵¹³ Clinical hypothyroidism is unusual and may be due to reduced TSH response to TRH. Whilst lithium causes a decreased thyroxine with increased TSH, carbamazepine causes a decrease in thyroxine with normal TSH.

Haematology – leucopaenia (may be reversed by lithium), thrombocytopaenia, agranulocytosis, aplastic anaemia, thromboembolism
 Others – oedema (dose-dependent), fever, proteinuria, lymphadenopathy, acute renal failure, cardiac conduction disorders³⁵¹⁴, hepatitis³⁵¹⁵, immunoglobulin deficiency (Hayman & Bansal, 2002)
 Overdose³⁵¹⁶ – tremor, excitement, seizures, hypo- or hypertension, diminished consciousness, EEG and ECG (including arrhythmias) changes

Carbamazepine-lithium combination: In general this combination is safe and well tolerated despite some reports of neurotoxicity, especially if the treatment is initiated at lower doses and increased with care. (Ballenger, 1988) Carbamazepine-induced leucopaenia may be reversed by lithium.

Valproate

Valproate (sodium valproate/Epilim) is useful in the treatment of mixed affective states and it may be safer than carbamazepine in those patients who have cardiac disease. (Brown ea, 2000) Low dose valproate (mean level of 32.5 micrograms/ml) may help the milder rapid-cycling patient or the person with cyclothymia but more severe bipolar cases may need antiepileptic doses (50-120 micrograms/ml). Other anticonvulsants will reduce valproate plasma levels and should such drugs be stopped the levels of valproate levels will increase. Valproate does not do this to other anticonvulsants because it doesn't induce liver enzymes. The combination of valproate and the carbapenems³⁵¹⁷ is not recommended because its leads to a rapid and significant drop in valproate levels. The same may apply to a combination of valproate and chitosan³⁵¹⁸, a common dieting agent. The combination of clonazepam and valproate may induce absence status in those patients with a history of absence seizures. Unlike carbamazepine, *valproate does not cause oral contraceptive failure*. Valproate has been combined with lithium and even with a combination of lithium and carbamazepine. (Denicoff ea, 1997) However, valproate can increase the levels of the 10,11-epoxide metabolite of carbamazepine to toxic levels. (Brown ea, 2000) Valproate can also increase lamotrigine levels, thereby increasing the risk of rash. The half-life of valproic acid is 6-16 hours, and there is 95% protein binding. Sodium valproate causes less GIT side effects than does valproic acid. It should be taken on a full stomach. Valproate can increase serum amylase and ammonia levels³⁵¹⁹, the latter being potentially important if there is liver disease. Aspirin should be avoided³⁵²⁰ in favour of paracetamol. The combination of valproate with antipsychotic drugs can potentially cause an encephalopathy with diffuse EEG slowing or an exacerbation of Parkinsonism. Erythromycin increases valproate levels. (Brown ea, 2000)

Divalproex³⁵²¹ sodium (Depakote) is an anticonvulsant drug that is absorbed into the bloodstream as valproate. It has been found to improve responsivity of refractory affective disorders (not necessarily including rapid cycling: Calabrese ea, 2005) to lithium or carbamazepine when it is added to the regimen. Divalproex sodium is probably safe in combination with lithium. (Granneman ea, 1996)

³⁵¹⁴ Quinidine-like action of this tricyclic drug: consider valproate for patients with heart disease who have bipolar affective disorder.

³⁵¹⁵ Less than 5% of patients experience a benign rise in liver enzyme levels and perhaps less than 1 in 10,000 patients experience a serious acute hepatic necrosis and then usually during the first weeks of therapy.

³⁵¹⁶ Following massive overdose, peak plasma concentrations may be reached on second or third day after ingestion.

³⁵¹⁷ Doripenem, ertapenem, meropenem, and imipenem (antibiotics).

³⁵¹⁸ Chitosan is found in crab exoskeleton and in fungal cell wall.

³⁵¹⁹ Inhibition of urea synthesis.

³⁵²⁰ Increased total and free valproate levels by displacing the drug from binding proteins.

³⁵²¹ This is a dimer molecule that dissociates in the GIT to form free valproate. It causes less GIT upset than valproate.

Side effects of valproateHair loss³⁵²²Severe nausea, vomiting³⁵²³, diarrhoea

Tremor (responds to beta-blockers), dizziness, sedation, ataxia, dysarthria, memory impairment

Weight gain

Persistent increase in liver transaminases (usually asymptomatic and normalises on stopping the drug)

Fatal liver damage (children under 10 years of age)

Pancreatitis (young children)

Thrombocytopaenia³⁵²⁴, inhibition of platelet aggregation, abnormal coagulation parameters³⁵²⁵Interference with thyroid function tests³⁵²⁶

Back pain

False test for ketones in urine

Valproate should be avoided in the presence of hepatic failure.

There may be CNS depression, especially in combination with agents such as alcohol. The association between valproate and polycystic ovaries (PCOS)³⁵²⁷ is complex and incompletely resolved, one study showing no association. (see Schatzberg ea, 2005, pp. 271, 272) However, Joffe ea (2006) found that over 10% of bipolar women on valproate had oligomenorrhoea or hyperandrogenism versus almost one-and-a-half percent bipolar females taking lithium or a different anticonvulsant. Ostacher and Tilley (2008, p. 663) present evidence for an association between PCOS and valproate and advise against employing valproate as a 'first-line' treatment of bipolar disorder in women of childbearing age.

There may be displacement of other protein-bound drugs, e.g. phenobarbitone, aspirin, phenytoin, and carbamazepine. Schaff ea (1993) suggest aiming for 50-100 mg/ml of serum.

Lamotrigine (Lamictal dispersible tablets)

A phenyltriazine that was noted to improve mood in epileptics, lamotrigine is thought to work in bipolar disorder by inhibiting excitatory presynaptic neurotransmitter release, especially glutamate. It also blocks sodium channels and 5-HT₃ receptors. Peak plasma concentration occurs 2-3 hours after ingestion, the half-life is about 30 hours, 55% is protein bound, bioavailability is 98%, first-pass metabolism is minimal, and an inactive glucuronide metabolite is formed in the liver and excreted in the urine. Lamotrigine crosses the placenta and is found in foetus and breast milk. Side effects include nausea, sedation, dizziness, headache, and diplopia. It seems to be weight neutral. Diarrhoea and

³⁵²² Rarely there may be loss of all body hair. Give vitamin preparation containing zinc and selenium. Severe alopecia may necessitate stopping the drug and hair re-growth (tends to be curly) may then take several months.

³⁵²³ Can be quite marked – give low dose to start, increase dose slowly, use enteric-coated tablets; H₂ antagonists may alleviate persistent GIT distress. (Stoll ea, 1991)

³⁵²⁴ Usually mild and reverses on reducing dose or stopping drug.

³⁵²⁵ E.g. low levels of fibrinogen.

³⁵²⁶ Disputed by Sit & Rothschild. (2002, p. 765)

³⁵²⁷ Also associated with obesity and epilepsy.

tremor are less than with lithium. Most lamotrigine-related rashes (occurring in 10% of patients) are of little clinical importance, but because rare cases can be very serious³⁵²⁸, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, it has been suggested that rash is an indication for stopping the drug. Certainly, where the face is extensively involved, where there is evidence of mucous membrane involvement³⁵²⁹, or where there are systemic symptoms³⁵³⁰ there is no choice but to stop the drug and to treat the case as an emergency. Slow titration of dosage may reduce the likelihood of serious rash developing. There are rare reports of blood and liver problems, which cannot as yet be directly attributed to lamotrigine. A few cases of breakthrough seizures, unexpected pregnancies³⁵³¹ and of menstrual bleeding disorders³⁵³² have been reported to GlaxoSmithKline in women on a combination of lamotrigine and the contraceptive pill. Anovulants decrease serum levels of lamotrigine and such levels may there rise on stopping the contraceptive pill. The half-life of lamotrigine is doubled by valproate³⁵³³ and halved by phenytoin and carbamazepine. Lamotrigine dose should be halved in the presence of valproate. Duncan ea (1998) called for more detailed studies of lamotrigine use in the affective disorders. A small, open, non-randomised report of lamotrigine being effective when added to clozapine in partially clozapine-responsive patients was conducted by Dursun and McIntosh.(1999) Goldsmith ea (2003) reviewed the lamotrigine literature and found that it may be good for bipolar depression but that it was without demonstrated efficacy for acute mania. Also, it was of limited efficacy in delaying time to manic/hypomanic episodes but it significantly delayed time to intervention for a depressive episode. Junker and Stodieck (1997) reported a case of lamotrigine-responsive clozapine-induced myoclonus. The starting dose is 25 mg daily for 2 weeks, followed by 50 mg daily for 2 weeks, gradually increasing to 200 mgs daily over 6 weeks (range in bipolar disorder: 50-300 mg/day). Higher doses give no additional efficacy. If the patient is also on valproate, start with 25 mg every second day (max. dose 100 mgs daily); if on carbamazepine, give 50 mgs daily to start (max. dose 400 mgs daily). Divided dosing can be used. If it is decided to stop lamotrigine the drug should be withdrawn slowly.

Verapamil (e.g. Isoptin, Verap)

Verapamil, a class I calcium antagonist, may be a useful treatment in acute mania.

Gabapentin (Neurontin)

Despite positive case reports, trials do not support use of this drug in the treatment of bipolar disorder³⁵³⁴.(Frye ea, 2000; Pande ea, 2000) However, it might be considered in the augmentation of other mood stabilising drugs in very anxious patients or in rapid-cyclers. It has found a niche in the management of anxiety, pain, and substance use disorders.

Antipsychotic drugs

Esparon ea (1986) performed a double blind crossover trial of depot flupenthixol (flupenthixol) in recurrent manic-depression. All patients stayed on lithium. Eleven patients completed the two-year trial. Flupenthixol appeared to have no prophylactic effect. Flupenthixol is nevertheless employed in depot injectable form in non-compliant patient with recurrent affective disorders by many clinicians.

Clonidine (Catapres, Dixarit)

Giannini ea(1986) found lithium to be more effective than clonidine in manic patients. Some patients on clonidine developed depression and hypotension.

³⁵²⁸ 0.1% of treated cases; especially in **children** or in **those also taking valproate**.

³⁵²⁹ As indicated by oral or lingual lesions or by complaints of dysuria.

³⁵³⁰ E.g. pyrexia or enlarged lymph nodes.

³⁵³¹ Lamotrigine may be associated with oral clefts in the offspring.

³⁵³² E.g. breakthrough bleeding.

³⁵³³ Increasing the rate of non-serious rash.

³⁵³⁴ Pfizer had to pay \$430 million for inappropriate marketing of gabapentin!

Clonazepam (Rivotril³⁵³⁵)

Clonazepam reduces lithium clearance. Sachs (1990) reported early claims that clonazepam reduced cycle frequency in bipolar affective disorder, was associated with fewer depressive episodes than when antipsychotic drugs were employed, and that neuroleptic-lithium combinations could be switched to a clonazepam-lithium combination without leading to an acute relapse.

Drug use in the elderly

This important subject is dealt with here for convenience. Various factors affect drug disposition in old people: age-related physiological changes, pathology, and therapeutic and environmental factors. Age-related physiological changes include absorption³⁵³⁶, distribution³⁵³⁷, metabolism³⁵³⁸, and excretion³⁵³⁹.

Some guidelines for prescribing drugs in the elderly

Take a careful drug history and check for use of over-the-counter drugs
 Be familiar with the effects of age on the pharmacology of drugs
 Strive to make a diagnosis before instituting therapy
 Use smaller starting doses
 Adjust the dose according to response
 Review the drug treatment plan regularly and keeping it simple
 Be alert to the possibility of iatrogenic illness
 Beware interactions between disease states and drugs.

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³⁵³⁵ Rivotril 1 mg/ml concentrate for solution for injection or infusion is also available.

³⁵³⁶ Changes in gastric pH, absorption surface, splanchnic blood flow, and gastric motility.

³⁵³⁷ Reduced cardiac output, total body water, lean body mass, and serum albumin; increased α 1-acid glycoprotein and body fat.

³⁵³⁸ Decreased hepatic mass and hepatic blood flow.

³⁵³⁹ Reduced renal blood flow, GFR, and tubular secretion.

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Antidepressant drugs³⁵⁴⁰

Brian O'Shea

'...successful treatment may require patients to tolerate side effects'.(APA, 2002)

'Before modern treatments, depressed patients typically spent one-fourth of their adult lives in the hospital and fully one-half of their lives disabled'.(Loosen & Shelton, 2008, p. 325)

Most antidepressants take 7-21 days before they cause subjective lifting of depressed mood. Sleep may improve immediately when a sedative antidepressant is given at night. Stimulating³⁵⁴¹ antidepressants (AD) should be given early in the day to prevent interference with sleep. Older people and children should normally commence on one-half to one-third of the adult starting dose³⁵⁴². A trial using adequate doses of antidepressants must be undertaken before describing depression as refractory, e.g. 300 mgs/day of imipramine or its equivalent³⁵⁴³. A therapeutic trial of an antidepressant should last for at least 6 weeks, with at least 4 weeks on the highest tolerated safe dose. Side effects will be better tolerated if it is explained that these are usually transient and that the drug will be reduced if significant improvement does not occur in about 6 weeks. Relapse may be due to non-compliance.(O'Shea, 1995) The initial dose is built up gradually. Maintenance treatment at the therapeutic dose for at least 6 months and then slowly reduced in case the episode of depression has not abated. The early stages of recovery from depression may be accompanied by a sufficient return of volition³⁵⁴⁴ to make suicide a real possibility³⁵⁴⁵. Some patients make the mistake of taking antidepressants on a p.r.n. basis. Studies of suicides suggest that antidepressants are either not prescribed at all or are given in sub-optimal dosage in many cases of depressive illness. The serum concentrations of antidepressants show a wide individual variation, are increased by antipsychotic drugs and are decreased by barbiturates. Depression in the elderly requires for its proper treatment a consideration of its wide variety of associated aetiological factors. Drug metabolism is less efficient in the elderly. The reader is advised to check an up to date data sheet from the manufacturer before prescribing a drug, especially where he or she is not very familiar with the product – this advice applies to all pharmaceuticals³⁵⁴⁶. Drugs that block noradrenaline uptake, like maprotilene, or 5-HT, like fluoxetine, appear to have equivalent antidepressant potency. Downregulation of

³⁵⁴⁰ A study of psychiatrists' outpatient prescribing practices in Rhode Island during 2001-2(Zimmerman et al, 2004) showed that their main considerations were avoiding specific side effects (esp. sexual dysfunction and weight gain), comorbidity (esp. GAD and panic disorder), and the presence of specific symptoms (esp. high anxiety, insomnia and fatigue). Prior response to treatment came next. Drug interactions or discontinuation syndromes were much less influential. In order of frequency, the prescribed drugs were citalopram (23.3%, N = 265), bupropion, sertraline, venlafaxine, mirtazapine, fluoxetine, paroxetine, nefazodone, TCAs, others/missing, and, in 0.4% (N = 4), MAOIs.

³⁵⁴¹ Often synonymous with non-sedating.

³⁵⁴² TCA effectiveness in children has been shown to equal that of placebo.

³⁵⁴³ Imipramine is the best studied of the TCAs and is often used for comparison with newer antidepressants.

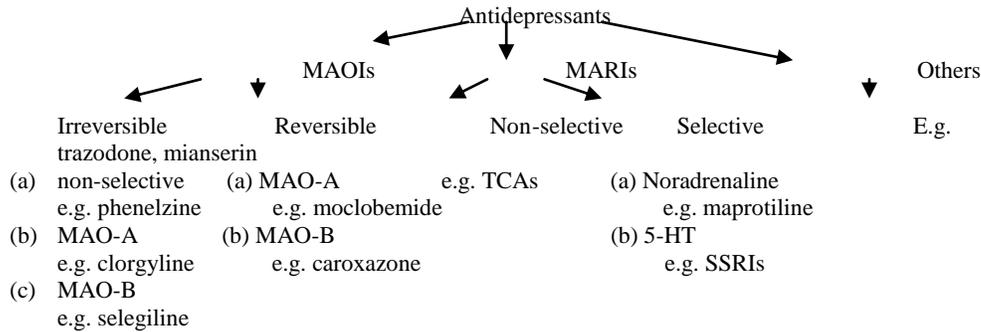
³⁵⁴⁴ Conative is synonymous with volitional.

³⁵⁴⁵ Simon et al (2006) found little evidence to suggest that newer antidepressants increase risk of suicide or serious suicide attempt.

³⁵⁴⁶ Zimeldine (Zelmid, derived from chlorpheniramine), the first SSRI, was removed from the market because of neurological problems (Guillain-Barré syndrome). The SSRI Femoxetine failed to reach the market. Another SSRI, indalpine, was withdrawn due to hepatotoxicity. Nomifensine was in use for seven years before its toxicity became apparent. Viloxazine, a bicyclic derivative of β -blockers that inhibits 5-HT uptake, was also withdrawn. Bupropion was temporarily withdrawn because of concerns over seizure induction.(Leonard, 2003, p. 190)

postsynaptic β -receptors is a very consistent finding after antidepressant treatment, and the same phenomenon has been reported with ECT and sleep deprivation. Researchers hold that one-third of patients placed on antidepressant drugs are non-responders, one-third are placebo responders, and the final third constitute responders.³⁵⁴⁷

Classification of antidepressant drugs



MAOI, monoamine oxidase inhibitor; MAO- monoamine oxidase; MARI, monoamine reuptake inhibitor; 5-HT, 5-hydroxytryptamine or serotonin; TCA, tricyclic antidepressant; and SSRI, specific (or selective) serotonin reuptake inhibitor.

Actions of antidepressant drugs (schematic)

Action on central serotonergic +/- catecholaminergic systems by reducing breakdown, blocking presynaptic (re-) uptake, or agonist/antagonist effects at receptor: **immediate** effect is increased availability of 5-HT +/- catecholamines



Down-regulation of presynaptic autoreceptors, alpha- and beta-noradrenergic receptors, and 5-HT₁ receptors: closer in time to **delayed** onset of clinical response (However, Mitchell [2006] and Tylee and Walters [2007] contend that antidepressants produce maximum improvement during the first 2 weeks, with some improvement in the first 3 days; also, Taylor et al [2006] found that SSRIs improved symptoms of depression by the end of week one with a decreasing rate of improvement for at least six weeks.)



Modulation of G proteins, second messenger systems, and gene expression: probably the **real reason** for efficacy/effectiveness*

*Protein phosphorylation within the cell is increased by chronic treatment with antidepressant drugs and this results in increased microtubule formation, which in turn may alter intraneuronal signal transduction. (Leonard, 2003, p. 166)

Tricyclic antidepressants (TCAs)

TCAs were still the most popular first preference antidepressants among senior Irish psychiatrists in 1991. (O'Shea, 1991) In fact, they may still be the most commonly used antidepressants world-wide. (Caturvedi, 1999) Tricyclics have no beneficial effects in euthymic subjects. TCAs are re-uptake inhibitors of monoamines (MARIs), preventing the re-uptake of neurotransmitters into the presynaptic neurone. Desipramine is a very strong re-uptake inhibitor of nor-adrenaline whereas clomipramine is a powerful

³⁵⁴⁷ The last third are said to occupy the 'efficacy window'. The narrowness of this window suggests that increased or decreased efficacy in comparative studies have to be large in order to be detected.

serotonin re-uptake inhibitor. The clinical utility of an IV infusion of clomipramine is debatable. (Loudon, 1993)

Following absorption, TCAs are metabolised by methylation and hydroxylation in the liver before they pass into the circulation where they are strongly bound to proteins. There is little to distinguish so-called slow release preparations from standard forms of TCAs.

TCAs can be subdivided into two groups on the basis of their sedative potencies: sedative (tertiary amine tricyclics - chiefly block 5-HT re-uptake; the higher the plasma concentration the greater is their antidepressant effect) and activating (secondary amine tricyclics - chiefly block noradrenaline re-uptake; the 'therapeutic window' effect leads to a situation where serum levels above or below a certain range fail to be therapeutic³⁵⁴⁸). Side chain demethylation converts tertiary amines to secondary amines and the latter to (inactive) primary amines.³⁵⁴⁹ Sudden cessation of tricyclics can lead to restless agitation, insomnia, headaches, vomiting and hyperhidrosis. A better guide to TCA toxicity than plasma level is the ECG. Excessive doses of TCAs can cause hypertension³⁵⁵⁰, cardiac arrhythmias, hallucinations, excitement, and seizures. TCAs impair conduction in the Bundle of His, causing tachycardia, arrhythmia, and heart block. Cardiac monitoring as well as stomach washout is indicated in cases of overdose.

O'Brien and Oyeboode (2003) have discussed the Brugada syndrome, a disorder of the Na⁺ channel and a cause of death (esp. during sleep) in Thai males.³⁵⁵¹

Donovan and Freeman (1990) believed that toxicity in TCA overdose has been over-emphasised when the benefits to patients from TCAs is considered.³⁵⁵² During the period 1993-7 in England and Wales 20% of all deaths from overdose and poisoning were antidepressant related. Whilst the number of such deaths increased by 18% during the same period, prescriptions for these drugs increased three times. 95% of antidepressant deaths were due to TCAs, especially dothiepin (dosulepin) and amitriptyline³⁵⁵³.

Lofepamine was relatively safe. The highest death rates were in males aged 30-44 years and in females aged 45-59 years. Very interestingly, such deaths were 2.5 times higher in the more socially deprived areas. In 28% of cases more than one drug was taken. (Shah et al, 2001)

Another study (Hawton et al, 2010), gathering data from disparate sources, found that TCAs (dosulepin [dothiepin] and doxepin were potentially more lethal than amitriptyline) were potentially more lethal than venlafaxine or mirtazapine, SSRIs being the potentially least lethal antidepressants (with citalopram having the highest case fatality among SSRIs).

³⁵⁴⁸ E.g. nortriptyline 50-150 ng/ml. The statistical strength of the therapeutic window concept is generally too weak to have much influence on clinical practice.

³⁵⁴⁹ Amitriptyline (Tryptizol, Lentizol, Triptafen, Laroxyl – half-life 9-36 hrs; active metabolite nortriptyline has half-life of 18-44 hrs), dothiepin (dosulepin: Prothiaden – half-life 14-24 hrs; active metabolite desmethyl-dothiepin has a half-life of 23-46 hours), trimipramine, and clomipramine (Anafranil) are sedative TCAs. Examples of activating TCAs are protriptyline (Concordin - most activating TCA) and nortriptyline (e.g. Aventyl).

³⁵⁵⁰ Inhibition of reuptake of adrenaline and noradrenaline; inhibition of uptake of guanethidine, bethanidine, clonidine and debrisoquine increases blood pressure by antagonising the hypotensive drug effect.

³⁵⁵¹ Mutation of the SCN5A gene leads to a reduction of inward Na⁺ depolarising currents. The main complication is ventricular fibrillation. The heart is structurally normal. The ECG shows right bundle-branch block and S-T segment elevation in chest leads V1-V3, but a normal QT interval. Overdose of TCAs (and possibly of antipsychotic drugs) may present with these features.

³⁵⁵² The UK fatal toxicity index (FTI: deaths/million prescriptions) for various antidepressants, according to Buckley and McManus (2002) are (FTI in brackets) TCAs in general (34.8), desipramine (200.9), amoxapine (93.5), dothiepin (53.3), amitriptyline (38.0), declining to nortriptyline (5.5), lofepramine (1.3), and protriptyline (0); for serotonergic drugs the FTIs are venlafaxine (13.2), clomipramine (12.5, a TCA), fluvoxamine (3), citalopram (1.9), sertraline (1.2), fluoxetine (0.9), paroxetine (0.7), and nefazodone (0 – withdrawn 2003: liver failure); FTIs for MAOIs are tranylcypromine (43.6), phenelzine (14.9), and iproniazid and isocarboxazid (both 0); and those for flupenthixol (0.4), tryptophan (0), and lithium (7.2). In a report by Cheeta et al, (2004) the standardised proportionate mortality rate (SPMR) for amoxapine was 10 compared to SPMRs of, for example, protriptyline 5, amitriptyline 1.8, dothiepin 1.7, lofepramine 0.1, moclobemide 2.2, tranylcypromine 2.5, phenelzine 1.1, SSRIs 0.1-0.3, venlafaxine 1.6, and trazodone 0.3.

³⁵⁵³ Deaths/100,000 prescriptions for TCAs, MAOIs and SSRIs were 5.3, 4.4 and 0.4 respectively.

Apart from nortriptyline, there are no definite therapeutic ranges for TCA plasma levels.³⁵⁵⁴ Such levels may still be useful to monitor compliance or to confirm toxicity. TCA levels should be measured when the drug has reached steady state, usually after 5-7 days, and about 10-14 hours (aim for 12 hours) after ingesting the last dose.

TCA's

(a) TCA groups

Tertiary amines (terminal methyl group on side chain; potent antagonists of alpha-1-adrenoceptors and muscarinic cholinergic receptors – more sedating and anticholinergic) – amitriptyline (a very effective drug with low tolerability), imipramine (Tofranil)³⁵⁵⁵, doxepin (originally seen as safe in heart disease, but low doses used, withdrawn November 2006), trimipramine, clomipramine

Secondary amines – desipramine, nortriptyline, protriptyline

Note: Tertiary amines are converted to secondary amines, so that the effect of the derived compound has to be added to the effect of the parent compound, e.g. imipramine, amitriptyline, and clomipramine are converted to desipramine, nortriptyline, and desmethylclomipramine respectively. Desmethylclomipramine is a more potent inhibitor of noradrenaline uptake than of 5-HT uptake.

(b) Side effects of TCAs

Anticholinergic: dry mouth³⁵⁵⁶, blurred vision³⁵⁵⁷, oesophageal reflux³⁵⁵⁸, constipation, urinary retention. Anticholinergic drugs can cause delirium.³⁵⁵⁹

Biliary: cholestatic jaundice

Cardiovascular: postural hypotension³⁵⁶⁰, tachycardia³⁵⁶¹, arrhythmias³⁵⁶², conduction defects, hypertension, cardiac failure, myocardial infarction,³⁵⁶³ ECG changes (prolonged PR + QRS, flat T, depressed ST), cardiomyopathy, and sudden death. Lofepramine (Gamanil) is *relatively* safe. Cardiotoxicity reaches significant proportions in people with pre-existent heart problems and in overdose. Some authors suggest that psychiatric illness may play a role in myocardial infarction and that this fact confounds the undoubted increase in adverse myocardial events in treated patients. (Thorogood *et al.*, 1992) Cannon *et al.* (1994) found that imipramine improved symptoms in patients with chest pain and normal coronary angiograms. They point out that 10-30% of patients undergoing cardiac catheterisation because of chest pain are found to have normal coronary angiograms. Astemizole (Hismanal), an anti-allergic drug (selective H1 antagonist) that prolongs the QT interval, may cause adverse events if combined with arrhythmogenic drugs like TCAs, antipsychotic drugs, and antiarrhythmics. TCAs may prevent uptake of adrenaline in local anaesthetics with consequent rise in blood pressure. Methylphenidate plus a TCA can cause hypertension.

Epilepsy: lowering of seizure threshold; it is suggested that clomipramine daily dosage be kept below 250 mg for that reason

³⁵⁵⁴ Therapeutic imipramine (plus desipramine) and desipramine levels of greater than 200 ng/ml and 125 ng/ml have been suggested.

³⁵⁵⁵ Imipramine (Tofranil), withdrawn 2006.

³⁵⁵⁶ Artificial saliva or hard sweets may help and attention to dental hygiene must be emphasised.

³⁵⁵⁷ Antidote: pilocarpine drops.

³⁵⁵⁸ Inhibited cardiac sphincter.

³⁵⁵⁹ 'Central anticholinergic crisis', e.g. with TCAs; use of an IV injection of physostigmine to bring about a rapid resolution of this crisis has been advocated, but the safety of such a treatment has been questioned because of possible adverse cardiac effects. In fact, physostigmine should only be used as a last resort.

³⁵⁶⁰ Relatively less likely with nortriptyline. (Roose *et al.*, 1981)

³⁵⁶¹ Rarely a significant problem with therapeutic doses. (Glassman & Bigger, 1981) but may be disconcerting.

³⁵⁶² Anoxia has been postulated to change TCAs from being antiarrhythmic to arrhythmogenic agents.

³⁵⁶³ Especially if TCA + age + stress. (Cohen *et al.*, 2000)

Eyes: increased intraocular pressure in narrow angle glaucoma; reduced lacrimation (antimuscarinic -predisposition to corneal infection/damage, esp. if contact lenses used)

Genitourinary: impotence, orchitis, hesitancy, retention, anorgasmia, and inability to ejaculate

Haematology: eosinophilia, leucocytosis, leucopaenia, and thrombocytopenia with purpura; agranulocytosis is a rare hypersensitivity reaction to TCAs found most commonly in elderly females in the second month of treatment

Metabolic: gynaecomastia, amenorrhoea, engorged breasts and galactorrhoea, hypoglycaemia, changes in AVP (ADH) output

Nausea: try changing commercial preparation

Neuropsychiatric: sedation³⁵⁶⁴, confusion, headache, insomnia, aggressiveness, agitation, nightmares³⁵⁶⁵, hallucinosis, EPS, dysarthria, nystagmus, myoclonus³⁵⁶⁶, peripheral neuropathy, tinnitus, exacerbation of schizophrenia due to excess dopamine (DA), hypomania* (The increase in DA may improve Parkinson's disease but a TCA + L-DOPA can cause agitation, tremor and rigidity.) Tremor may respond to beta-blockers.(Bharucha & Sethi, 2004, p. 243)

Liver: elevated transaminases and alkaline phosphatase

Rapid cycling of mood disorders

Sexual: diminished libido, delayed or absent orgasm, and absent or retrograde ejaculation.³⁵⁶⁷

Skin: sweating, rashes (mild rashes might be treated symptomatically but anything more significant should lead to withdrawal³⁵⁶⁸ of the drug – avoid drugs that are metabolites of the offending agent, i.e. desipramine/imipramine or nortriptyline/amitriptyline)

Weight gain: chiefly associated with amitriptyline, chlorpromazine, clozapine, olanzapine, and lithium; it might be due to an increased appetite due to effects on noradrenergic pathways, thirst and the drinking of 'soft' or other drinks, or resistance to ADH. Ideally, the patient should be weighed regularly, including a baseline measurement before starting treatment. Dietician should advise on a low-carbohydrate diet (watch sodium in lithium preparations). Patient should drink water (not sugary drinks). If possible, reduce the dose of the drug. It has been suggested that depot haloperidol may cause less increase in weight than other depot antipsychotic drugs. It has also been suggested that trifluoperazine and haloperidol are superior in this regard than are chlorpromazine, thiothixene or thioridazine. Avoid anorectic drugs if possible (may exacerbate psychosis and cause valvular heart disease). H2-blocking agents have been suggested for weight gain with olanzapine, as has amantadine.(Symmetrel, up to 300 mg/day: Graham ea, 2005)

Note: If the antidepressant mainly inhibits noradrenaline reuptake, as is the case with desipramine, relapse may follow addition of the noradrenaline synthesis inhibitor α -methyl paratyrosine.

*Lewis and Winokur (1982), and a number of later authors, believed that TCAs probably did not 'cause' a manic switch and that it was really a spontaneous swing that was being observed. Stoll ea (1994) found that mania secondary to antidepressants to be milder and of shorter duration than spontaneous mania and they suggested that MAOIs and bupropion may be associated with milder manic states than either TCAs or fluoxetine.

Contraindications to TCAs include prostatism, glaucoma, ischaemic heart disease, epilepsy, mania, and a history of recurrent ODs - risk must be weighed against likely benefit in individual cases. Bunney (1978) estimated that the risk of occurrence of hypomania is 11% with MAOIs (particularly with tranylcypromine) and about 8% with TCAs.

³⁵⁶⁴ This can be antihistaminic with doxepin or amitriptyline, or alpha-1-adrenergic blockade as with trazodone.

³⁵⁶⁵ Perhaps due to an anticholinergic action.

³⁵⁶⁶ This is usually mild. In problematic cases reduce TCA dose or add clonazepam.

³⁵⁶⁷ Dry orgasm.

³⁵⁶⁸ Preferably slow to avoid cholinergic rebound.

Of lofepramine (half-life of 2-3 hrs), an imipramine analogue and a tertiary amine with little anticholinergic potential, one third is broken down to desipramine³⁵⁶⁹. Lofepramine acts like a secondary amine³⁵⁷⁰. It has and a *relatively* low cardiotoxicity potential compared to other TCAs. Uncommonly, patients on lofepramine have become icteric during the first two months of treatment, and this disappears if the drug is stopped.

Clomipramine, a powerful cause of impotence, is useful in phobic and obsessional states³⁵⁷¹; high doses may activate withdrawn schizophrenics. Imipramine is useful in the short-term management of enuresis.(see later)

Amoxapine (Asendis - a demethylated metabolite of loxapine)³⁵⁷² is thought to block noradrenaline reuptake and to a lesser extent it may block 5-HT reuptake. There is also DA blockade by its metabolite.³⁵⁷³ There are minimal anticholinergic effects. Side effects include seizures, minor ECG changes, hypotension, hyperprolactinaemia³⁵⁷⁴, malignant neuroleptic syndrome, EPS and tardive dyskinesia. According to Buckley and McManus (1998) amoxapine had the highest fatal toxicity index³⁵⁷⁵ of all antidepressants! Children bind less TCA to protein and have less fat, into which the lipid soluble drug can penetrate, and hence are at greater risk than adults of toxic effects.

TCAs may reduce the antihypertensive effects of guanethidine, debrisoquine, bethanidine, a clonidine by interfering with the reuptake mechanism of noradrenergic neurones.

Patients with delusional affective disorder seem to respond less well to TCAs or to lithium than do those without delusions.

Sudden withdrawal from TCAs³⁵⁷⁶ can lead to a 'cholinergic rebound syndrome'³⁵⁷⁷ consisting of anxiety, dizziness, nausea, vomiting, gastric upset, diarrhoea, sweating, headache, and neck pain. TCA abstinence symptoms in children who were on moderate or high doses include flu-like symptoms with nausea, vomiting cramps, headaches, and muscle pains. Also described are social withdrawal, hyperactivity³⁵⁷⁸, depression, agitation, and insomnia. Withdrawal symptoms from TCAs may be prevented by very gradual tapering of dosage or by adding low doses of an anticholinergic drug³⁵⁷⁹.

Nicotine and carbamazepine lower plasma TCA levels. Oestrogens, cimetidine, sodium valproate, and many antipsychotic drugs and SSRIs increase TCA levels.

Notes on the management of enuresis: *This problem is more often one for paediatricians and child mental health care workers than for general adult psychiatrists. Nevertheless, the adult prevalence of this problem is about 1%. Behavioural methods of treatment include restricting fluids before bedtime, scheduled nocturnal waking to pass urine, and awards (praise, stars, etc) for dry nights. The bed and pad method (wetting sets off an alarm) is very effective (in children it is important that parents arise as well). TCAs,*

³⁵⁶⁹ Desmethylimipramine or desipramine, a secondary amine with a half-life of 12-24 hrs.

³⁵⁷⁰ Inhibits noradrenaline re-uptake but not 5-HT.

³⁵⁷¹ Obsessional traits predict good response to fluvoxamine.(Anseau ea, 1991)

³⁵⁷² **Amoxapine:** A dibenzoxazepine tetracyclic (sometimes described as a secondary amine TCA – it has a tricyclic structure with a fourth ring attached by a –N bond) that is said to be relatively safe from the cardiovascular point of view. It is said to be less likely than other TCAs to cause hypotension. Amoxapine is rapidly absorbed after oral ingestion. Amoxapine is converted to loxapine by the liver. Its main metabolite, 8-hydroxy-amoxapine, which has antipsychotic properties, has a 30-hour elimination half-life (8 hours for amoxapine).

³⁵⁷³ Relative antidepressant affinities for D2 receptors range from 5.6 for amoxapine to 0 for venlafaxine.(Richelson, 2001) The D2 antagonism of amoxapine may exacerbate Parkinson's disease.(Fava & Papakostas, 2008, p. 607)

³⁵⁷⁴ Galactorrhoea, amenorrhoea, and impotence.

³⁵⁷⁵ Surpassed by desipramine in their 2002 paper.

³⁵⁷⁶ Or low potency phenothiazines.

³⁵⁷⁷ Exposure of upregulated postsynaptic Ach receptors. However, this explanation has been challenged and serotonergic mechanisms may be involved.

³⁵⁷⁸ Hypomania with sudden withdrawal.(Schatzberg ea, 2005, p. 111)

³⁵⁷⁹ E.g. diphenhydramine 25 mg bid-tid.

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especially imipramine about 2 mg/Kg nocte (avoid desipramine), are effective, although relapse is common in practice on stopping the drug, particularly if the dose is reduced too quickly. Desmopressin (DDAVP, an antidiuretic hormone/vasopressin analogue: Desmospray, Desmotabs), MAOIs, and carbamazepine have also been shown to help. Oxybutynin (Cystrin, Ditropan, Renamel), an anticholinergic-antispasmodic, may improve daytime enuresis by relaxing the detrusor muscle. Anticholinergic drugs per se are not effective. There are many other approaches, e.g. ultrasound detection of bladder size.

Monoamine oxidase inhibitors (MAOIs)

The classical indications for MAOIs are atypical depression or reverse negative symptoms: mood reactivity, irritability, rejection hypersensitivity, hypersomnia, hyperphagia, and psychomotor agitation. Early studies of MAOIs used low doses. Higher doses are superior to placebo and, whether or not the depression has endogenous features, MAOIs are equivalent in effectiveness to TCAs.

Two subgroups of MAOIs

*Hydrazine*³⁵⁸⁰ e.g. phenelzine (Nardil)

Non-hydrazine e.g. tranylcypromine (Parnate³⁵⁸¹)

MAOIs inhibit MAO. This process starts in the gut wall, continues in the liver, and ends in the brain. The dose needs to be increased until CNS side effects occur, such as sedation with phenelzine or postural hypotension with tranylcypromine. Tranylcypromine is stimulant and euphoriant. Phenelzine (Nardil), which is sedative, is started in a dose of 15 mgs BID and cautiously increased if required to 15 mgs QID (dose range 45-90 mgs/day).

Hepatocellular damage with jaundice from hydrazines is rare except in alcoholics. If an adequate trial of one MAOI does not work, other MAOIs probably won't work either. (Schatzberg et al, 2005, p. 123) MAOI serum levels are not related to therapeutic effect. A platelet MAO suppression of more than 80% may be necessary for optimal therapeutic response, although this requirement is not universally accepted dogma. Slow acetylators have low levels of acetylase, an autosomal recessive trait. The clinical relevance of acetylator status is less certain than it was. (Leonard, 2003, p. 85)

Side effects of MAOIs

Abuse for feeling of euphoria, e.g. tranylcypromine³⁵⁸².
Dry mouth, constipation, nausea, postural hypotension³⁵⁸³, blurred vision, colour blindness³⁵⁸⁴, tremor, peripheral neuropathy, electric shock-like sensations³⁵⁸⁵, impotence, urinary retention, weight gain, leucopaenia, sweating, migraine made worse or initiated, hypomania, hepatocellular jaundice (especially iproniazid³⁵⁸⁶ and other hydrazines³⁵⁸⁷),

³⁵⁸⁰ NH₂NH₂.

³⁵⁸¹ A cyclopropylamine formed by substitution of isopropyl side chain of amphetamine with a cyclopropyl one.

³⁵⁸² Amphetamine is one of the metabolites of tranylcypromine. Marangell et al (2003) suggest a two-week interval between stopping phenelzine and starting tranylcypromine because of the amphetamine-like nature of the latter drug.

³⁵⁸³ Possibly due to DA accumulation in sympathetic cervical ganglia where it acts as an inhibitory neurotransmitter with consequent reduction in peripheral vascular tone. (Leonard, 2003, p. 170) Salt tablets or fludrocortisone may help.

³⁵⁸⁴ This is uncommon. Pheniprazine, an early MAOI, was withdrawn because it caused transient red-green colour blindness from Retrobulbar neuritis.

³⁵⁸⁵ These may respond to clonazepam. Peripheral neuropathy usually responds to vitamin B6 50-100 mg/day.

³⁵⁸⁶ Fox, a chemist, at Hoffmann-La Roche Labs in New Jersey, looking for anti-TB drugs, synthesised isoniazid from isonicotinic acid; iproniazid was synthesised from isoniazid; Irving Selikoff (1915-92) reported the improved mood induced by the latter as a toxic effect!

³⁵⁸⁷ Hydrazine: two linked NH groups.

exacerbation of liver disease, exacerbation of gluten enteropathy with gluten-containing preparations.

Peripheral oedema of the dependent type³⁵⁸⁸ may occur with TCAs, MAOIs, or with phenothiazines.

Phenelzine may lower pseudocholinesterase and prolong neuromuscular blockade.³⁵⁸⁹

Hypertensive crisis – hypertension, headache, vomiting, sweating, and, potentially, intracranial haemorrhage or myocardial infarction.

Notes: Constipation should be treated with a bulk laxative, such as methylcellulose (Celevac) or bran.

Avoid SSRIs, clomipramine, fenfluramine, and buspirone.

Patients on non-selective MAOIs who are stung by a bee (causes MAO-A inhibition in GIT) may develop a hypertensive crisis (increased tyramine absorption leading to pressor effect).

It has been suggested that patients taking MAOIs carry a 10 mg nifedipine (calcium channel blocker) tablet to chew or dissolve under the tongue at the first sign of hypertensive reaction (sudden fatigue or a pounding bilateral occipital headache). Some workers believe that the risks associated with nifedipine are irrelevant compared with a hypertensive crisis. Others point out that nifedipine use in such circumstances may cause myocardial infarction and would strongly suggest that it not be used. The best drugs are still chlorpromazine, 25-50 mg IM, or phentolamine (Rogitine), 5 mg IV. Marangell ea(2003) suggest that due to risks of cardiac arrhythmias or severe hypotension phentolamine should be given in a place where such adverse outcomes can be managed (e.g. A & E department).

Ginseng, found in herbal remedies, may cause headache, tremor, insomnia, or mania if taken with MAOIs.

Drug interactions may occur with sympathomimetics³⁵⁹⁰, TCAs³⁵⁹¹, α -methyl dopa and reserpine may cause central excitation, insulin and oral hypoglycaemic drugs³⁵⁹², alcohol and barbiturates³⁵⁹³. MAOIs block the metabolism of phenytoin, which may put the patient at risk for phenytoin toxicity. Antihistamines can be co-prescribed with a MAOI as long as there are no accompanying sympathomimetics. Narcotic analgesics are a different story. Pethidine³⁵⁹⁴ should always be avoided because of the risk of a fatal excitatory reaction, but morphine is safe to use. There are two distinct forms of MAOI/narcotic interaction: excitatory³⁵⁹⁵ and depressive³⁵⁹⁶. The only analgesics to have elicited the excitatory response are pethidine (meperidine/Demerol) and, possibly, dextromethorphan³⁵⁹⁷. Remick ea (1987) found no evidence of hazard with the combination of a general anaesthetic with a MAOI. They also felt that it was unwarranted to stop MAOIs for two weeks before ECT. Peden (2000) saw little evidence for stopping psychotropic drugs before anaesthesia, but advises forewarning the anaesthetist.

³⁵⁸⁸ Fluid retention causes puffy hands and swollen ankles (an effect on local blood vessels has also been postulated). Salt restriction may help.

³⁵⁸⁹ When the anaesthetist requires it, stop phenelzine 10-14 days before elective procedures requiring succinylcholine. However, phenelzine therapy is no longer seen as a contraindication to surgery or ECT.(Alpert ea, 2004, p. 257)

³⁵⁹⁰ Ephedrine, nasal decongestants, cough and cold cures – asthma inhalers can cause problems, except for pure steroid preparations.

³⁵⁹¹ Hypertensive crisis – especially imipramine, desipramine, and clomipramine.

³⁵⁹² Increased sensitivity to these drugs may cause severe hypoglycaemia.

³⁵⁹³ Increase in central depression.

³⁵⁹⁴ Meperidine [Demerol] in USA.

³⁵⁹⁵ Sudden agitation, unmanageable behavior, headache, hypo- or hypertension, rigidity, fits, pyrexia, and coma - possibly due to central serotonergic overactivity.

³⁵⁹⁶ Respiratory depression, hypotension, and coma - inhibition of hepatic microsomal enzymes by MAOI with consequent accumulation of non-metabolised narcotic.

³⁵⁹⁷ Present in OTC cough syrups.

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The *cheese reaction* (Blackwell et al, 1967) is due to the presence in food of the indirect sympathomimetic tyramine³⁵⁹⁸. Any foods subject to decomposition may contain pressor amines. Tyramine releases adrenaline and NA and causes severe headache, fever, muscle spasm, and even cerebral or subarachnoid bleeding. Among foods to be avoided are cheese, meat (i.e. if not fresh) and meat and yeast extracts (Oxo, Bovril, and Marmite) fortified wines, any non-fresh food, broad bean pods (not the beans themselves), pickled herrings, and venison. Fava beans contain L-dopa and should be avoided. Chianti is an oft-quoted offender. Small quantities of some wines, non-tap beers (bottled and canned) and sherries may be taken in safety. Avoid tap beers. Tyramine can be present in processed drinks involving yeast, even if alcohol is absent. Therefore, patients on MAOIs should avoid tapped alcoholic and non-alcoholic beers. The list of restricted foods is potentially very long (banana skins, caviar, etc) and an up-to-date warning card must be obtained from the dispensing pharmacist. Tyramine content of food varies by sample, country and region. (Pies & Shader, 2003, p. 262) Schatzberg et al (2005, p. 119) advise against eating Chinese food because of ingredients such as sherry and soy sauce.

Management of a hypertensive crisis

Oral nifedipine (calcium channel-blocker): 10 mg, often normalises blood pressure within minutes

Chlorpromazine

Phentolamine (Rogitine) 5 mgs IV: this alpha-adrenergic blocker should only be used in a suitable hospital setting because it may be associated with cardiac arrhythmias or significant hypotension

Other steps: suxamethonium, a ventilator and tepid sponging

On stopping a TCA one should wait at least three days before starting a MAOI. The opposite switch demands an interval of at least seven days³⁵⁹⁹ (5-6 weeks when stopping tranylcypromine). When starting a MAOI + TCA combination wait for one week after stopping either class of drug. Each drug is given in small doses and slowly increased together (some authorities start the TCA first and gradually add the MAOI). Only some combinations are relatively safe, e.g. phenelzine (Nardil) and amitriptyline (Tryptizol) or trimipramine (Surmontil). *Tranylcypromine and clomipramine is an extremely dangerous combination*. Changing from a MAOI to a TCA is more dangerous than is the opposite manoeuvre (one may need suppression of much MAO for a reaction). Adding a MAOI to a TCA is safer than the opposite manoeuvre. When switching from a hydrazine MAOI like phenelzine to a non-hydrazine MAOI like tranylcypromine (a derivative of amphetamine) one should wait at least 2 weeks after the first drug is withdrawn because the latter drug inhibits noradrenaline uptake and causes dextroamphetamine-type sympathomimetic effects which may cause toxicity if the second drug is instituted too early. (Nies, 1982) SSRIs should never be prescribed with MAOIs and fluoxetine takes 5-6 weeks to leave the system (leave about 2 weeks for other SSRIs). Not everyone considers the risks of combined antidepressants to be as serious as these notes suggest. For example, Pare et al (1982) felt that a TCA/MAOI combination may be safer than prescribing MAOIs alone as it seems to reduce the risk of causing a 'cheese' effect. However, there is no universal consensus on the usefulness of TCA/MAOI combination therapy. (Kennedy & Joffe, 1989)

Moclobemide: Classic MAOIs bind very strongly and irreversibly to MAO, resulting in a complete and prolonged inhibition of MAO. Moclobemide (Manerix³⁶⁰⁰) is a selective MAO-A inhibitor and substituted benzamide. Tyramine can compete with it for the enzyme, making moclobemide much less likely to cause a hypertensive crisis, although

³⁵⁹⁸ Or other offenders such as DOPA.

³⁵⁹⁹ For moclobemide and selegiline leave 1 week after stopping either drug before giving another antidepressant. (Lam & Mok, 2008, p. 54)

³⁶⁰⁰ Aurorix in USA.

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some authors (e.g. Livingston, 1995) would suggest full MAOI precautions as for the non-selective drugs. Full MAO activity is restored within 24 hours. Some authors do not accept that moclobemide is as effective as TCAs and the classic MAOIs. (e.g. Howland & Thase, 2002) It is said to be non-toxic to the liver. Moclobemide plasma levels are increased by cimetidine (Tagamet). Moclobemide has little effect on body weight, reaction times (as in driving), short-term memory, or arousal. Its action lasts for 8-16 hours, the elimination half-life is 1-2 hours, and it is 50% bound to plasma proteins. Moclobemide may be associated with raised levels of liver enzymes of no clinical relevance. The usual dose is 300 mg/day in 2-3 divided doses (max. 600 mg/day³⁶⁰¹). Lower doses are given in the presence of severe hepatic disease or drugs that inhibit microsomal mono-oxygenase activity (e.g. cimetidine). Do not use it with pethidine, SSRIs (danger of serotonin syndrome) or 5-HT precursors, or in the presence of thyrotoxicosis or phaeochromocytoma. The combination of clomipramine and moclobemide has been reported to cause a serotonin syndrome. Hypertensives should avoid a large amount of old ripe cheese³⁶⁰². Indirectly acting sympathomimetics and pethidine should be avoided during anaesthesia. Side effects include insomnia, headache, dizziness, nausea, and confusion (rare). Controversially, (Freeman, 1993) Fahy (1993) suggested that moclobemide-treated patients may become very excited and have experiences of unreality. Moclobemide causes increased effects of opiates and ibuprofen. Very little appears in breast milk and a washout period is not required before starting TCAs. Overdose causes agitation, aggressiveness and behavioural changes. The efficacy of the RIMAs has questioned. (Leonard, 2003, p. 171)

Brofaromine, selegiline, toloxatone and chlorgyline are other selective MAOIs.

Selegiline (Eldepryl or -deprenyl) is a selective and irreversible MAO-B inhibitor that potentiates brain DA function. Selegiline is derived from metamphetamine; indeed, like tranlylcypromine, it is metabolised to L-amphetamine and L-methamphetamine in the body. It was not viewed as a useful antidepressant and was used for Parkinson's disease. However, it has become available as a patch-delivered antidepressant (Emsam: 6 mg/24 hr) in the US. It is said not to cause a tyramine reaction with no need therefore for dietary restrictions³⁶⁰³. The most important adverse effects are confusion and psychosis. Selegiline protects against methyl-phenyl-tetra-hydro-pyridine (MPTP) in animals. MPTP is converted by MAO-B to MPP that selectively destroys nigrostriatal DA neurones. *Do not use SSRIs or add an MAO-A³⁶⁰⁴ inhibitor (moclobemide) if the patient is taking selegiline*, and be cautious in the use of TCAs. Lauterbach (2000) suggests discontinuation of selegiline for at least two weeks (5 weeks for fluoxetine) before starting another antidepressant because of reported fatalities due to drug interactions. Abrupt discontinuation of selegiline may lead to nausea, dizziness, and hallucinations. (Schatzberg et al, 2005, p. 125)

DA and tyramine are common substrates for both types of MAO (-A and -B). Noradrenaline and 5-HT are substrates for MAO-A, and phenylethylamine and benzylamine are substrates for MAO-B. Non-selective MAOIs like tranlylcypromine exert significant effects on both types of MAO and are therefore more likely to give rise to a cheese reaction. Because moclobemide preferentially inhibits MAO-A it interferes less with the metabolism of tyramine.

Because irreversible MAOIs form a permanent covalent bond between the MAO enzyme and the inhibitor their duration of action is equal to the time required for renewal of the enzymes. A single dose can last for several days.

³⁶⁰¹ At very doses, such as 900 mg/day, moclobemide also inhibits MAO-B.

³⁶⁰² Otherwise there is not the same embargo as with the older MAOIs.

³⁶⁰³ However, other authorities suggest that dietary precautions are required for higher (9 or more mg) but not lower (6 mg) doses of selegiline.

³⁶⁰⁴ RIMA + selegiline = non-selective MAOI!

In the case of reversible MAOIs, the duration of action is dose-related to the elimination half-life. High affinity substrates can displace the inhibitor from the enzyme. Also, MAO-B is still left to metabolise the ingested tyramine³⁶⁰⁵.

Selective/specific serotonin reuptake inhibitors (SSRIs)

The SSRIs (unlike TCAs) do not share a common structural moiety. They have a range of structures encompassing monocyclic, bicyclic, tricyclic and tetracyclic configurations. The most potent SSRI (at inhibiting 5-HT uptake) is paroxetine, and the most selective (for serotonin) SSRI is citalopram followed by sertraline.³⁶⁰⁶ The therapeutic action of SSRIs may not be as simple as inhibition of reuptake of serotonin at the presynaptic receptor.³⁶⁰⁷

Tamoxifen may reduce serum TCA levels and the activity of tamoxifen itself may be reduced by SSRIs.(Jin ea, 2005) Paroxetine used in association with tamoxifen may be associated with an increased risk of death from breast cancer, at least in older women.(Kelly ea, 2010)

Nausea may limit compliance with SSRI therapy,(Dowling ea, 1990) and taking the drug with food may help in this regard. Also, nausea often diminishes with time on the drug. Low dose cisapride may relieve such nausea, perhaps via antagonism of 5-HT₃ receptors³⁶⁰⁸. Ginger tea is found helpful by some patients. Ondansetron³⁶⁰⁹ may also be helpful³⁶¹⁰. SSRIs, fluoxetine more than paroxetine, may interfere with sleep and taking the bulk of the dose in the morning may reduce this effect. Longterm use of SSRIs may be associated with side effects that are not obvious during acute treatment, e.g. sleep problems, sexual dysfunction, and weight gain,(Sherman, 1998) and perhaps amnesia.(Joss ea, 2003) Prolactin levels may rise in SSRI-treated patients, more often in women than in men, which has implications for fracture risk, especially in older people.(Fava & Papakostas, 2008, p. 600) *Never combine an MAOI with an SSRI.(vide supra)* Procarbazine³⁶¹¹ and linezolid³⁶¹² are MAOIs and therefore should not be given to someone on an SSRI. SSRIs may cause EPS such as Parkinsonism or even TD.(Gerber & Lynd, 1998) The reason why TCAs and SSRIs can induce EPS may relate to the fact that 5-HT normally and tonically inhibits brainstem DA function. There are suggestions that SSRIs can 'reveal' tardive dyskinesia in those patients previously exposed to antipsychotic drugs or to exacerbate such disorders. SSRIs can worsen the tremor of lithium as well as the EPS caused by antipsychotic drugs, bupropion, and psychostimulants. The minimum effective dose of the SSRIs produces about 80% inhibition of platelet serotonin uptake in most patients. Agents increasing serotonin availability³⁶¹³ can, especially if combined with an SSRI, potentially lead to a serotonin syndrome with delirium, agitation, restlessness, diarrhoea, hyperthermia, rapidly changing vital signs, ataxia, dysarthria, rigidity, myoclonus, hyperreflexia, and possibly

³⁶⁰⁵ As well as MAO-A from which the RIMA - reversible inhibitor of MAO-A - moclobemide is displaced.

³⁶⁰⁶ Relative affinities for blocking the 5-HT transporter among selected antidepressants are: paroxetine 800, clomipramine 360, sertraline 341, fluoxetine 120, citalopram 86, fluvoxamine 45, venlafaxine 11, and doxepin 1.5.(Richelson, 2001)

³⁶⁰⁷ Other actions that may be important include blockade of somatodendritic autoreceptors (an early effect is downregulation/desensitisation of such receptors), reduced impulse flow in the axon, a delayed increase in presynaptic release of 5-HT (a candidate for the true therapeutic action), and downregulation of postsynaptic receptors (perhaps conferring tolerance to side effects).

³⁶⁰⁸ **Cisapride** (Prepulsid) can cause QT elongation and, according to Mitchell ea (2002, p. 1199), it was taken off the US market for this reason. It was formally employed in anorexia nervosa.

³⁶⁰⁹ 5-HT₃ receptor antagonism.

³⁶¹⁰ Mirtazepine blocks 5-HT₃ receptors and causes less GIT upset than SSRIs. Some practitioners co-prescribe mirtazepine with SSRIs for a short period.

³⁶¹¹ A treatment for blood malignancies.

³⁶¹² Linezolid is an antibacterial oxazolidinone that is a non-selective MAOI.

³⁶¹³ Lithium, MAOIs such as chlorglyline or phenelzine, tryptophan, clomipramine, etc.(Keck & Arnold, 2000)

coma and death³⁶¹⁴.(Edwards, 1992) Fluoxetine may cause a serotonin syndrome even when the patient stops taking it if another serotonergic drug is added! Overdose³⁶¹⁵ of MAOIs has caused serotonin syndrome, as have carcinoid and oat cell carcinomas. The drug(s) should be stopped (resolution usually follows quickly). BZDs or a cooling blanket may be required. 5-HT antagonists (e.g. cyproheptadine, 8-32 mg/day) or (for its 5-HT1A antagonism) propranolol may be indicated in some cases.

Headache, occipital and pounding, is associated with SSRIs, and may occur more frequently with continued use.(Frazer, 1997) Pharyngitis, dyspnoea, serum sickness and alopecia are uncommon adverse effects of SSRIs. All SSRIs can cause hyponatraemia (see Ul Haque ea, 2010) via inappropriate ADH secretion (in one series SIADH mainly occurred in the over-65s on SSRIs, usually starting on day 13; TCAs, such as lofepramine, have also been reported to cause hyponatraemia). SIADH usually resolves over several weeks after stopping the offending drug. As well as stopping the offending drug, fluids should be restricted. Symptoms of SIADH include headache and lethargy. Apart from hyponatraemia there is an increase in renal excretion of sodium and the urine is hyperosmotic. In severe cases (delirium, seizures, or coma) IV sodium chloride is required.

SSRIs inhibit CYP2D6 and there increase TCA and antipsychotic drug concentrations. SSRIs may increase the effects of warfarin with a tendency to bleed without a change in prothrombin time. Nemeroff ea (1996) warn that inhibitors of cytochrome P450 3A4³⁶¹⁶ should preferably be avoided in patients on terfenadine, astemizole, alprazolam or triazolam or in patients receiving midazolam as a component of anaesthesia. Side effects are very similar for each SSRI and are most pronounced early in treatment. Sexual dysfunction is common in patients on SSRIs³⁶¹⁷. Moclobemide has less sexual side effects, the opposite applying to SSRIs and venlafaxine. However, clomipramine and SSRIs can be used to treat premature ejaculation, and trazodone has been used to treat erectile dysfunction. Sexual side effects of antidepressants might be approached by dose reduction, changing the drug, a drug holiday, or remedial therapy.(Mir & Taylor, 1998) The latter may take several forms.³⁶¹⁸

Strategies for managing sexual side effects of antidepressants (Rothschild, 1999)

Reduce dose
Weekend drug holidays for short half-life drugs
Change the antidepressant
Take medication after coitus
Cyproheptadine
Bethanacol
Amantadine
Yohimbine
Buspirone
Bupropion

Seizures may occur with any SSRI. Rash in SSRI-treated patients is usually urticarial and may rarely include fever, arthralgia, and lymphadenopathy. If a rash occurs the SSRI should be stopped. Mydriasis has been reported with paroxetine and a combination of

³⁶¹⁴ That being said, this author (or many others, e.g. Hendrickx & Floris, 1991) has experienced no significant problems among patients treated with lithium and an SSRI.

³⁶¹⁵ Beware of the patient who takes an overdose of multiple antidepressants, e.g. SSRI + TCA or MAOI!

³⁶¹⁶ Especially fluoxetine, fluvoxamine, and nefazodone.

³⁶¹⁷ Consider changing to trazodone.

³⁶¹⁸ If the problem is increased serotonergic transmission (e.g. SSRIs) one could try the antihistamine cyproheptadine (which has 5-HT2 antagonist activity). However, according to Meston & Frohlich,(2002) cyproheptadine can interfere with the antidepressant effects of SSRIs. Granisetron (5-HT3 antagonist) may improve SSRI-induced anorgasmia. Yohimbine (α_2 antagonist and α_1 agonist) for fluoxetine-induced impotence or anorgasmia. Amantadine (DA agonist) for ejaculatory difficulties or (taken 5-6 hrs before intercourse) anorgasmia secondary to SSRIs.

mydriasis and uneven pupils³⁶¹⁹ with paroxetine and sertraline.(Barrett, 1994) SSRIs inhibit hydroxylase enzymes and may thus increase TCA plasma levels by a factor of four. The combination (TCA + SSRI) can cause hypertension and/or the serotonin syndrome. Yawning and spontaneous orgasm are rare side effects of SSRIs. Overdose of SSRIs may cause agitation, vomiting and seizures. The SSRIs are finding an ever-expanding list of applications, e.g. depression³⁶²⁰, depression associated with anxiety, obsessional states, social phobia, bulimia nervosa, and premenstrual syndrome. Efficacy is similar for all the SSRIs³⁶²¹.(Edwards & Anderson, 1999) SSRI discontinuation rates may be no different from those for newer TCAs and heterocyclics.(Hotopf ea, 1997) although they compare favourably in this regard with the older TCAs. The SSRIs are expensive compared to TCAs (Song ea, 1993) although their side effect profile seems more acceptable to consumers. Withdrawal (discontinuation) symptoms are least likely with fluoxetine³⁶²² and most likely with paroxetine. Such symptoms potentially include short-lived (usually start after 48 hours and resolve within 3 weeks³⁶²³) dizziness, nausea, vomiting, diarrhoea, myalgia, fatigue, anxiety, headache, agitation, insomnia, unusual dreams, sweating, tremor, vertigo, hallucinations, electric shock-like sensations, and depersonalisation. There has also been a report of a neonatal withdrawal reaction. SSRIs should be withdrawn gradually, especially those with shorter half-lives. Some authors suggest giving one dose of fluoxetine to attenuate withdrawal from shorter acting serotonergic antidepressants.(Marangell ea, 2003) Short-term use of a benzodiazepine is another possible strategy.(Marangell ea, 2003)

An increase in anxiety early on in treatment with an SSRI often proves to be transient. It may be due to hypersensitive 5-HT_{1A} receptors that normalise with continued treatment. Use of low starting doses (e.g. fluoxetine 10mg mane) may avoid much of this problem, but the patient should be forewarned. The patient should be monitored for agitation.(Geddes & Cipriani, 2004)

An *apathy syndrome*, which may be subtle, has been ascribed to SSRIs. There is an inability to 'experience feeling', good or bad.(Price ea, 2009) It may respond to dose reduction or switching to a non-serotonergic antidepressant such as bupropion. When depression lifts but anhedonia persists, drug-induced apathy should be considered.

Fluoxetine³⁶²⁴ (Prozac, Prozamel, Norzac, Fluzac, Bellzac) is an SSRI that is unrelated chemically to either TCAs or tetracyclics. It is not to be combined with MAOIs or tryptophan. The starting and usual therapeutic dose for depression dose is 20 mgs/day.³⁶²⁵ Fluoxetine is taken in the morning. The parent drug has a long elimination half-life of 2-3 days. So also has its major active metabolite, desmethylfluoxetine (7-9 days), also a potent and specific 5-HT re-uptake inhibitor. In the elderly the clinician can prescribe 10 mg/day or 20 mgs every second day.

³⁶¹⁹ Anisocoria.

³⁶²⁰ Many clinicians view them as indicated in 'mild/moderate' cases only – some studies have reported superior efficacy for TCAs(, e.g. Danish University Antidepressant Group[1990; Roose ea, 1994]) – but see Montgomery ea's meta-analysis(1994), who found similar efficacy between both groups with greater dropout rates for TCAs secondary to side effects; see also Montgomery & Johnson.(1995)

³⁶²¹ Kirsch ea (2008) meta-analysed data on randomised, double-blind, placebo-controlled trials conducted on patients with DSM major depression (measured with HRSD) treated with fluoxetine, venlafaxine, nefazodone, and paroxetine submitted to the FDA for licensing purposes. Drug-placebo differences increased as a function of initial severity: no difference at moderate levels and a relatively small difference at the very severe end of the severity scale. Timonen and Liukkonen (2008), on the other hand, whilst acknowledging that 'most' of the trials are sponsored by the pharmaceutical industry, suggest that there is 'robust' evidence for the efficacy of these drugs, and NICE recommends that we try SSRIs first for depression.(National Institute for Clinical Excellence, 2004) A possible reason for the Kirsch ea (2008) result might be an excessively wide variety of problems under the heading of 'depression' or, more fundamentally, an excessively short follow-up of 6 weeks.

³⁶²² Long half-life of parent and norfluoxetine/desmethylfluoxetine.

³⁶²³ Different sources give different timescales (e.g. starts within 24 hours, peaks days 5 to 6, and resolves within a fortnight) so it is difficult to be exact.

³⁶²⁴ The dose of the sustained release formulation of Prozac (Prozac Weekly) was 90 mg once weekly.(Schmidt ea, 2000; Miner ea, 2002) However, Eli Lilly announced its withdrawal from the market in mid-2008.

³⁶²⁵ Prozac liquid contains 20 mg/5 ml.

Five weeks must pass after stopping fluoxetine and starting a MAOI and more than 2 weeks after stopping a MAOI and starting fluoxetine, probably up to 6 weeks for tranylcypromine.

Fluoxetine inhibits the metabolism of TCAs and BZDs. Seizures have been reported in those patients receiving both a TCA and fluoxetine. Fluoxetine is extensively metabolised in the liver and excreted by the kidneys. Fluoxetine can reduce weight (albeit transiently), and can cause anorexia, agitation, and insomnia. Paton and Ferrier (2005) discuss the differential affinities of various antidepressants on the serotonin transporter: high for clomipramine, fluoxetine, sertraline, and paroxetine; intermediate for citalopram, fluvoxamine, and venlafaxine; and low for doxepin, mirtazepine³⁶²⁶, moclobemide, and nortriptyline. Fluoxetine decreases granular storage of serotonin in platelets that can lead to an increase in bleeding time.³⁶²⁷ Rarely there may be bruising or melaena. Upper GIT bleeding is a potential problem with SSRIs and venlafaxine, made much more likely if NSAIDs, ticlopidine or aspirin is added to the regimen.(Anonymous, 2004; de Abajo & Garcia-Rodriguez, 2008) It is suggested that the bleeding time be checked before elective surgery if the patient is on fluoxetine³⁶²⁸. Caution has been urged when prescribing SSRIs in any patient on a treatment that increases the risk of bleeding.(Anonymous, 2003a) Paton and Ferrier (2005) suggest using gastroprotective agents³⁶²⁹ in certain groups of SSRI-treated patients, e.g. history of bleeding, elderly, those on NSAIDs or aspirin, but not in those on SSRIs alone.

Starting in 1990, reports started appearing alleging that fluoxetine caused the emergence of serious suicidal preoccupation in depressed patients³⁶³⁰. The evidence is that fluoxetine probably is no more likely to be culpable in this regard than any other antidepressant,(e.g. Murphy & Kelleher, 1994; Khan et al, 2003; Jick et al, 2004; Geddes & Cipriani, 2004; Martinez et al, 2005; Tauscher-Wisniewski et al, 2007) especially in adults. Not all studies agree, however.(Fergusson et al, 2005) An important point is that suicidality may increase transiently in depressives when volition returns as depression lifts and self-harm may be related to variables other than depression or its treatment, e.g. family discord or substance abuse.(Brent et al, 2009) Interestingly, it has been advocated for agitated depression. However, the debate continues about the suicidogenic and withdrawal propensities of SSRIs in general.(Anonymous, 2003b; Leonard, 2004; Cato, 2005; Gunnell et al, 2005; Hall, 2006; Gibbons et al, 2006) Hypomania or mania occurs in a few percent of treated patients. There is less agreement that fluoxetine doesn't cause increased levels of hostility and aggression.(Anonymous, 1992) although the same has been said of TCAs. Also, SSRIs can cause akathisia, itself associated with suicidal ideation. Fluoxetine can cause hypoglycaemia and its side effects can mimic hypoglycaemia. According to Katona et al,(1995) the combination of lithium and fluoxetine causes neurotoxicity no more often than the combination of lofepramine. The combination of pimozide and fluoxetine can lead to bradycardia and/or delirium. Withdrawal of fluoxetine can potentially lead to hyperglycaemia. The anorectic and weight reducing properties and reduced incidence of anticholinergic side effects of fluoxetine may be of use in diabetes mellitus. Nevertheless, its use in diabetics should be carefully monitored.

³⁶²⁶ This 6-azo derivative of mianserin has more potent effects on the 5-HT system than has mianserin.

³⁶²⁷ 5-HT release from platelets augments their aggregation.

³⁶²⁸ But see Irish Medicines Board(2000) for a broader warning about SSRIs.

³⁶²⁹ H2 antagonists, proton pump inhibitors, or misoprostil.

³⁶³⁰ The American FDA warns of suicidality in relation to all antidepressants, but the risk of suicide is much higher in untreated depression.(Friedman & Leon, 2007) The Irish Medicines Board (2008) states that young adults in particular should be warned that they may feel suicidal during antidepressant treatment and that they should seek help immediately if they begin to feel that way; also a friend or close relative should be in the know and keep any eye on them; also, this precaution applies even if the reason for prescribing an antidepressant is for a disorder other than depression, e.g. anxiety.

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Fluoxetine, controversially (Pfeffer, 2007), is the only SSRI recommended by the FDA³⁶³¹ and the Committee on Safety of Medicines for use in children³⁶³². (Ramchandani, 2004; Geddes & Cipriani, 2004; Bennett ea, 2005)

Paroxetine (Seroxat, Parox, Meloxat; Paxil in USA) plasma levels are increased by phenytoin. The half-life is 21-24 hours. There are no active metabolites and little effect on weight. The starting dose is 20 mg daily (10, 20 and 30 mg tablets are available; the liquid form contains 20 mg/ml). Paroxetine, a phenylpiperidine, is relatively sedative (paroxetine is the most sedative SSRI, fluoxetine the least sedative) and, because of its relatively short half-life, it has a stronger propensity to be associated with withdrawal symptoms (dizziness, sweating, tremor) on cessation of therapy relative to fluoxetine. Paroxetine should not be stopped abruptly except on medical advice. Serotonin syndrome, akathisia, gastrointestinal bleeding, and hyponatraemia are possible with paroxetine. Dystonia has been recorded, especially early in treatment. As is common with many antidepressants, sweating can occur early in treatment. A few cases of stupor have been reported in the literature, (Lewis ea, 1993) as has transient or chronic hepatitis, (Benbow & Gill, 1997) and digitalis intoxication. (Yasui-Furukori & Kaneko, 2006) Ghaemi (2003, p. 243) cautions against the use of paroxetine in the elderly because of its anticholinergic potential. GlaxoSmithKline issued letters in June 2003 and July 2005 stating that paroxetine was not to be used in persons under 18 because of adverse events³⁶³³ and problems during tapering of paroxetine³⁶³⁴, all being reported at a frequency of at least 2% of patients and occurring at a rate of at least twice that of placebo. However, already successfully treated under 18s could complete a course a course of paroxetine. It should be noted that Jick ea (2004) who found no difference in suicidal behaviours in paroxetine-treated 10-19 year olds compared to those given fluoxetine, amitriptyline, or dothiepin. GlaxoSmithKline issued a communiqué in May 2006 to the effect that paroxetine use during the first trimester of pregnancy is associated in some epidemiological studies with a small increase in cardiovascular malformations (VSD and ASD).

Fluvoxamine³⁶³⁵ (Faverin) is said to inhibit the neuronal uptake of 5-HT with little or no effect on catecholamines. It has a low incidence of side effects, apart perhaps from GIT upset. Unlike TCAs, it has no clinically important cardiovascular effects.

Side effects of fluvoxamine

Nausea, vomiting, indigestion, diarrhoea
Dizziness, somnolence
Headache
Anxiety
Palpitations
Rash

The dose is 2 tablets taken at night to start. Plasma levels of drugs metabolised by the P450 system³⁶³⁶ may be increased. Fluvoxamine is a particularly potent inhibitor of CYP1A2, thus increasing plasma levels of drugs such as TCAs and mirtazapine. *It can increase clozapine levels at least 5 times.* (Olesen & Linnet, 2000) Silver ea(2003) reported improvement in primary negative symptoms of schizophrenia with fluvoxamine.

³⁶³¹ This led to reduced SSRI use in adults (Valuck ea, 2007) and children (Libby ea, 2009) and an increase in SNRI use in adults. (Libby ea, 2009)

³⁶³² Children and adolescents metabolise SSRIs faster than adults and may require doses in excess of those given to adults to achieve a clinical response. Gibbons ea (2006) found that higher rates of SSRI prescribing was associated with lower suicide rates in children and adolescents. See Gavin ea (2008) for discussion and Emslie ea (2008) for evidence for fluoxetine preventing relapse of major depression in children and adolescents.

³⁶³³ Decreased appetite, tremor, sweating, hyperkinesia, hostility, agitation, emotional lability (crying, mood fluctuations), self harm, suicidal thoughts, and attempted suicide.

³⁶³⁴ Nervousness, dizziness, nausea, emotional lability, and abdominal pain.

³⁶³⁵ An aralkyl ketone with a half-life of 22 hours.

³⁶³⁶ E.g. TCAs, phenothiazines, type Ic anti-arrhythmics, debrisoquine and sparteine.

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Sertraline³⁶³⁷ (Lustral, Seretral, Serlo, Bellsert) is said to little or no sedative effect. Plasma half-life is 26 hours. 98% is bound to plasma proteins. Its active metabolite, N-desmethyl-sertraline, has a half-life of 2.5-4.5 days. Starting dose is 50 mg/day and the maximum dose is 200 mg/day. Sertraline may be the least likely SSRI to be stopped by the patient.(Edwards & Anderson, 1999)

Citalopram (Cipramil, Citalopram Teva, Citrol, Cipralam, Ciprapine, Bellcital), a bicyclic with a half-life of 33 hours, is a 5-HT re-uptake inhibitor that is given once daily in 20-60 mgs doses, or 10-30 mgs in the elderly. The metabolites of this racemic compound are desmethylcitalopram (one-third the level of the parent compound in plasma) and didesmethylcitalopram (lower levels). Citalopram is a weak inhibitor of CYP2D6 and drug interactions do not appear to be a major problem. In particular, there seems to be no interaction with alcohol. The clinical effect is thought to be due mainly to citalopram itself. Its metabolites are less potent and enter the brain less readily.

Side effects of citalopram

Dry mouth
Somnolence
Nausea, diarrhoea
Sweating
Tremor
Ejaculatory failure

There have been some fatalities, especially when combined with alcohol or sedative drugs.(Edwards & Anderson, 1999) Citalopram prolongs the QTc in dogs.

Escitalopram oxalate (Lexapro) is the S-enantiomer of citalopram³⁶³⁸. The S-enantiomer of citalopram is an SSRI whereas the R-enantiomer is thirty times less active on the transporter.(Hyttle ea, 1992) It is as powerful an antidepressant as citalopram (Burke ea, 2002; Kennedy ea, 2006) and is better than placebo.(Wade ea, 2002) It binds to a specific site on the 5-HT receptor and to a site common to other SSRIs.(Leonard, 2007) Nausea may occur, but it tends to subside with continued use. Escitalopram appears to have a low potential for drug interactions via impaired P450 enzymatic activity.(Wade ea 2002) Depression is treated with 10 mg once daily (max. 20 mg). Panic disorder is treated with 5 mg per day for one week, then 10mg daily (max. 20 mg).

Sibutramine (Reductil) is a monoamine re-uptake inhibitor active against noradrenaline and 5-HT and to a lesser extent against dopamine, and it rapidly down-regulates both beta-adrenergic receptor binding as well as the noradrenaline - stimulated adenylate cyclase system. Sibutramine is structurally related to amphetamine and is marketed as an anti-obesity drug. The hypophagic effect may stem from activation of 5-HT_{2C} receptors. In trials, this putative antidepressant, at doses of 60 mgs, which is considered to be high, increased the mean arterial blood pressure by 7.8 mm. Hg. (p < 0.01) and the heart rate by 7.9 beats / minute (p < 0.01). There is some evidence that sibutramine may alleviate weight gain in patients treated with olanzapine.(Henderson ea, 2005)

Other new antidepressants

Venlafaxine (Efaxor XL, Efaxil XL, Ireven, Venlafaxine Teva, Vedixal, Venlofex, Venlift, Vedixal XR, Venex XL, Velift XL, Vensir XL)

³⁶³⁷ 1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine.

³⁶³⁸ It comes as 5 mg, 10 mg, 15 mg and 20 mg tablets.

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The phenylethylamine venlafaxine, a SNRI (serotonin and noradrenaline reuptake inhibitor) has an elimination half-life of 3-7 hours. It is O-demethylated to the active metabolite O-desmethylvenlafaxine, which has a half-life of 8-13 hours and is equipotent to the parent compound. Most psychotropic drugs are 80-95% bound to plasma proteins, except venlafaxine (15-20%) and O-desmethylvenlafaxine. In descending order of potency venlafaxine inhibits reuptake of 5-HT, noradrenaline, and DA.³⁶³⁹ Venlafaxine appears to be primarily serotonergic in lower doses and dopaminergic in doses over 300 mg daily.

Side effects of venlafaxine

Nausea (36% at first, 12% or placebo level at 3 weeks)

Headache

Insomnia (espc. in higher doses)

Somnolence

Dry mouth

Dizziness

Constipation

Asthenia

Postural hypotension (disputed)

Nervousness and sweating

Syncope (rare: may relate to a genetic sodium channel mechanism: Schatzberg ea, 2005, p. 78)

Extrasystole during ECT³⁶⁴⁰

Dose-dependent sustained hypertension (3% of treated patients)

Seizure (0.2%)

Rash (4%)

Impotence (7%)

Reversible increases in liver enzymes (0.5%)

Weight gain (<1%)

GIT bleeding (especially if also taking NSAIDs: de Abajo & Garcia-Rodriguez, 2008)

Venlafaxine, with the exception of escitalopram (Fava & Papakostas, 2008, p. 603), may be more potent than the SSRIs. It may have better efficacy and be better tolerated than imipramine. Venlafaxine may be superior to fluoxetine for anxiety associated with depression. It may be more effective than SSRIs for depression.(Smith ea, 2002) The usual starting dose is 37.5 mg bid. This can be increased after some weeks to 75 mg bid if needed. It should be taken with food. There are intermittent (IR) and extended (XR – given once daily) release preparations. Efexor XL is a once daily dosage formulation (recommended dosage, 75 mg/day; can be increased to 150 mg/day; max, 225 mg/day). The dose should be halved in the presence of moderate renal or hepatic failure. Reduced doses are not usually required in the elderly. Because of lack of data, venlafaxine is contraindicated in pregnancy (give advice to women about contraceptive measures), during lactation, and with MAOIs (*wait 2 weeks after stopping a MAOI and 7 days after stopping venlafaxine*). It is contraindicated in persons less than age 18 years (because a small number have developed hostility and suicidal ideation), uncontrolled hypertension, and in cases with a very high risk of ventricular arrhythmia.³⁶⁴¹ Lithium reduces the renal clearance of venlafaxine. There have been a number of reports of venlafaxine withdrawal symptoms.(Anonymous, 2003b) There is a suggestion that venlafaxine should be prescribed only by practitioners with a special interest in mental health.(Eaton, 2004)

³⁶³⁹ Cf. Stahl(2000) for illustrated account of how these actions might be translated into mRNA production.

³⁶⁴⁰ In patients with treatment-resistant depression on > 300 mg/day and receiving propofol.(Gonzalez-Pinto ea, 2002)

³⁶⁴¹ It should be noted that Martinez ea (2010) found that pharmacological doses of venlafaxine are not associated with an increased risk of potentially fatal arrhythmias.

NICE suggests that an ECG and blood pressure measurement be carried out before starting venlafaxine.

*Desvenlafaxine*³⁶⁴² (Pristiq)

Also known as O-desmethylvenlafaxine, this new SNRI is available in the USA as a 50 mg extended-release tablet. It is a synthetic form of the venlafaxine metabolite O-desmethylvenlafaxine. It has been found to be effective and tolerated in the treatment of major depression (DeMartinis et al, 2007) and may be useful for vasomotor menopausal symptoms. The blood pressure should be monitored and the dose reduced or the drug withdrawn if a persistent rise in pressure is found.

Adverse effects of desvenlafaxine

Nausea, dry mouth, anorexia, constipation, asthenia, insomnia, somnolence, nervousness, dizziness, sweating, problems with ejaculation/orgasm

Rare: hyponatraemia/SIADH, interstitial lung disease, eosinophilic pneumonia, serotonin syndrome, mydriasis

*Reboxetine*³⁶⁴³ (Edronax)

This selective noradrenaline reuptake inhibitor (NARI) has a low affinity for alpha-adrenergic and muscarinic receptors and no effect on DA uptake. It has low toxicity in animals. Because the half-life is 13 hours, reboxetine is given twice daily (4 mg twice daily to start and this may be increased to 10 mg/day after 3-4 weeks). A lower dosage is indicated in the frail elderly (2 mg bid) and in those with severe renal impairment, excretion being mainly via the kidneys. Reboxetine is rapidly absorbed after ingestion and food does not affect its bioavailability. Reboxetine is 97% bound to plasma protein, 92% in the elderly. 78% is excreted in the urine. Avoid reboxetine with MAOIs, macrolide antibiotics, fluvoxamine and azole anti-fungals. CYP2D6 is only involved at very high doses of reboxetine.

Side effects of reboxetine

Dry mouth
Headache/migraine
Dizziness
Gastrointestinal upset
Constipation
Sweating
Orthostatic hypotension (at higher doses)
High blood pressure³⁶⁴⁴
Tachycardia
Insomnia

³⁶⁴² 50 mg daily in adults. Adjust for renal/hepatic dysfunction.

³⁶⁴³ Structurally similar to viloxazine (withdrawn from market) and fluoxetine.

³⁶⁴⁴ It occurs in some cases, especially in people with SCL6A2 variant of noradrenaline transporter.

Paraesthesiae
Impotence (with higher doses)
Spontaneous ejaculation (very rare)
Urinary hesitancy/retention (latter with higher doses)
Less common: agitation, nervousness, anxiety, somnolence, and tremor
Cardiac rhythm problems (especially increased rate) and conduction disorders (small percent of elderly patients)
Seizures (rare – stop the drug)

There is some evidence that reboxetine may attenuate weight gain in olanzapine-treated schizophrenic patients. (Poyurovsky et al, 2003) It may be particularly useful in apathetic, anergic depressives.

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Mirtazapine (Zispin, Zispin SolTab³⁶⁴⁵, Mirap, Mirap Orodispersable, Mirtall, Mirzaten, Mirtazapine TEVA, Zismirt Orotab³⁶⁴⁶, and, in US, Remeron)

Mirtazapine is a noradrenergic and specific serotonergic (NaSSA) antidepressant and a 6-aza derivative of mianserin. Mirtazapine increases noradrenergic transmission by blocking α 2-autoreceptors. It also enhances 5-HT transmission via two synergistic mechanisms: increased serotonergic cell firing and blockade of alpha-2-adrenergic heteroreceptors. It specifically increases 5-HT1-mediated transmission because it blocks 5-HT2 and 5-HT3 receptors, leaving 5-HT1 receptors unhindered. The usual dose is 30 mg (15-45) nocte.

Adverse effects of mirtazapine

Sedation³⁶⁴⁷

Dry mouth

Increased appetite and weight (probably due to blockade of 5-HT2C receptors)

Constipation

Rare: orthostatic hypotension, mania, seizures, tremor, myoclonus, oedema, acute bone marrow suppression (neutropaenia is commoner than agranulocytosis³⁶⁴⁸), and increased serum levels of transaminases

Increased psychomotor effects of BZDs and alcohol

Raised serum cholesterol and triglyceride levels in some patients (APA, 2002, pp. 497 & 513)

The literature is somewhat conflicting regarding whether mirtazapine mitigates the sexual side effects of SSRIs (Schatzberg et al, 2005, p. 89) but it is generally seen as helpful in such situations. (Lloyd, 2007, p. 78) Binding to plasma proteins is only 85%. Mirtazapine should not be given for the first two weeks after stopping MAOIs. It has a similar effect on sleep architecture to amitriptyline. REM latency and stages 3 and 4 sleep are increased. Overdose leads to prolonged sedation and is treated by gastric lavage and support.

Duloxetine (Cymbalta)

³⁶⁴⁵ Zispin SolTabs (15 mg and 45 mg) dissolve in the mouth.

³⁶⁴⁶ Orodispersible 15 mg, 30 mg, 45 mg tablets.

³⁶⁴⁷ Because of recruitment of noradrenergic effects at higher doses, sedation may lighten as the dose rises to 30 mg/day or more.

³⁶⁴⁸ Avoid concomitant clozapine or carbamazepine.

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This combined 5-HT and noradrenaline reuptake inhibitor³⁶⁴⁹ is metabolised by CYP1A2 and the polymorphic CYP2D6, followed by conjugation. 96% is bound to plasma proteins. Metabolites are excreted principally in the urine. Like venlafaxine, it may diminish diabetic neuropathic pain³⁶⁵⁰.

Potential side effects of duloxetine

Nausea, dry mouth, constipation, diarrhoea

Sweating

Reduced appetite and weight

Insomnia, fatigue, somnolence/sedation/dizziness

Decreased libido, hot flushes³⁶⁵¹, anorgasmia, erectile dysfunction, ejaculatory delay/dysfunction

Tremor

Blurred vision, mydriasis (*risk of narrow-angle glaucoma*³⁶⁵²)

Hyponatraemia (rare, esp. elderly)

Tinnitus

Strong CYP1A2 inhibitors³⁶⁵³ raise duloxetine plasma levels. Smoking reduces duloxetine plasma levels by 50%. Use of duloxetine in pregnancy has to be based on a careful risk-benefit analysis; its use in breastfeeding women is not advised. The starting and therapeutic dose is 60 mg o.d. (dosage shown to be effective in prophylaxis of major depression: Perahia *et al.*, 2006) and the maximum dose is 120 mg, given in divided doses. There are 30 mg and 60 mg capsules. Little is known about use of duloxetine in the elderly. Since it is extensively metabolised (oxidation followed by conjugation and then the metabolites are excreted in urine) significant hepatic³⁶⁵⁴ and renal disease (creatinine clearance < 30 ml/hr) are contraindications to duloxetine use. Blood pressure should be monitored in cases of hypertension or cardiac disease. Avoid duloxetine with non-selective, irreversible MAOIs³⁶⁵⁵. It is not advisable to combine duloxetine with St John's Wort. Caution is required with concomitant use of SSRIs, clomipramine, venlafaxine, triptans, tramadol, pethidine, and tryptophan. The sucrose in the capsule can cause problems in people with fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency.

Discontinuation symptoms with duloxetine

Dizziness

Nausea

Vomiting

Insomnia

Nightmares

Headache

Anxiety

Irritability

Paraesthesia

³⁶⁴⁹ Venlafaxine is mainly serotonergic at lower doses but duloxetine strongly inhibits 5-HT and noradrenaline transporters in all clinical doses.

³⁶⁵⁰ Leonard (2006) has described duloxetine as 'venlafaxine at a lower dose'.

³⁶⁵¹ Interestingly, venlafaxine and SSRIs may decrease hot flashes due to tamoxifen.

³⁶⁵² Avoid use of duloxetine in patients with uncontrolled narrow-angle glaucoma.

³⁶⁵³ Fluvoxamine, ciprofloxacin, and enoxacin.

³⁶⁵⁴ There have been reports of hepatitis, hepatomegaly, raised liver enzyme levels, and cholestatic jaundice. It is suggested that duloxetine be avoided in heavy drinkers.

³⁶⁵⁵ Risk of serotonin syndrome: wait 2 weeks after stopping MAOI/at least 5 days after stopping duloxetine/lesser, but not absent risk with selective, reversible MAOIs like moclobemide.

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Duloxetine (*Yentreve*)³⁶⁵⁶ appears to be efficacious for female stress urinary incontinence. Manufacturer's data suggests that duloxetine causes urinary hesitancy in less than 1% of males. Elderly males should be monitored for this. (Schatzberg ea, 2005, p. 78) Naturally, one duloxetine preparation should not be combined with a second such preparation!

Review of duloxetine (Anonymous, 2007)

Published evidence for comparative efficacy insufficient in depression or diabetic peripheral neuropathic pain

Regarding stress incontinence - only prescribed for cases with 14 or more episodes/week where pelvic floor exercises are poorly effective or where surgery is unsuitable/undesirable

Duloxetine in elderly (recurrent) major depressives v placebo (Raskin ea, 2007)

Improved cognition, depression, and some pain measures; safe and well tolerated

Escitalopram v duloxetine in major depression (Wade ea, 2008)

24-week, randomised, double-blind, fixed dose

Escitalopram 20 mg/day vs duloxetine 60 mg/day

Greater improvement in symptoms at week 8 with escitalopram

Both drugs equal efficacy at 24 weeks

Withdrawal from study due to adverse effects greater with duloxetine

Milnacipran (Ixel)

This inhibits 5-HT and noradrenaline reuptake to an equal degree. 25 mgs twice daily or 50 mgs once daily is given during the first week, the recommended dose thereafter being 50 mgs twice daily for adults and elderly. It is glucuronidated and is not metabolised by P450 enzymes. It is comparable in efficacy to TCAs and, at least in severe cases, possibly better than SSRIs in major depression. (Montgomery, 2003) The main adverse effect is dysuria due to adrenergic receptor stimulation in the urinary tract. It should therefore be used with care in people with prostatic obstruction. (Kasper ea, 2001)

Tianeptine (Stablon)

This atypical tricyclic may have anxiolytic effects in major depression. (Lepine ea, 2001)

It modulates the HPA axis and glutamate and doesn't affect 5-HT uptake. (Leonard, 2007)

The dose is one tablet thrice daily (twice daily in elderly or with renal insufficiency). It should not be combined with MAOIs.

Side effects (uncommon and generally not severe)

Pain (epigastric, abdominal, precordial, muscular, back)

Dry mouth, anorexia, nausea, vomiting, flatulence

Insomnia, drowsiness, nightmares, asthenia

Tachycardia, extrasystoles

Vertigo, headache, faintness (lipothymia), tremor

Respiratory discomfort

Lump in the throat

Hot flushes

Agomelatine (Valdoxan)

Agomelatine³⁶⁵⁷ (Valdoxan) is a melatonergic (M1 and M2)³⁶⁵⁸ agonist and selective antagonist of 5-HT_{2C} receptors³⁶⁵⁹ and is active in several animal models of depression.

³⁶⁵⁶ 40 mg b.i.d., or 20 mg b.i.d. if side effects are troublesome.

³⁶⁵⁷ See vol. 21, suppl. 1, February 2006 (Montgomery SA, ed.) of *Internat Clin Psychopharmacol* 2006 for a fuller discussion.

Loo ea (2002) used a double-blind design comparing three different doses of agomelatine (1, 5 and 25 mg once daily) with placebo over an 8-week treatment period. Paroxetine was used as the study validator. 711 patients with a baseline mean score of 27.4 on the 17-item HAM-D were included. On the pivotal analysis, the mean final HAM-D total score demonstrated agomelatine 25 mg to be statistically more effective than placebo.³⁶⁶⁰ Agomelatine 25 mg alleviated anxiety associated with depression, as measured on *Hamilton Anxiety Scale*. Paroxetine was found to be effective on pivotal analysis and most of the secondary criteria used to validate the study methodology and population. Agomelatine, whatever the dose, showed good acceptability with a side-effects profile close to that of placebo. The starting dose in adults is 25 mg/day, increasing to 50 mg nocte after 2 weeks if response is inadequate. Patients on agomelatine should have *LFTs done at baseline, 6 weeks, and 24 weeks, and thereafter when clinically indicated*. Agomelatine is metabolised by CYP1A2 and to a lesser extent by CYP2C9. Fluvoxamine and ciprofloxacin, both being CYP1A2 inhibitors, increase agomelatine levels. Therefore, CYP1A2 inhibitors should not be co-prescribed with agomelatine. Lesser CYP1A2 inhibitors, such as oestrogen, should be prescribed with caution. Nausea and dizziness are common and usually transient ADRs associated with agomelatine. Other side-effects include migraine, headache, adverse effects on sleep, GIT upset, fatigue, sweating, and back pain. Erythematous rash and hepatitis are rare ADRs. Insufficient information is available concerning pregnancy and breastfeeding.

*St John's Wort*³⁶⁶¹

St John's Wort (SJW) contains at least 10 diverse chemicals that may possess psychotropic effects, such as hypericin. SJW probably works on several neurotransmitters, including serotonin³⁶⁶². It is unlikely to possess MAOI activity, but caution is advised if the patient is taking MAOIs and other antidepressants because of the rare possibility of a serotonin syndrome. A serotonin-like syndrome or hypertensive reaction, generally non-fatal, is possible when SJW is combined with serotonergic drugs as varied as SSRIs, venlafaxine, nefazodone, dextromethorphan, and pethidine. SJW is generally well tolerated. Mania may be induced in bipolar patients. Possibly by inducing P450 (CYP3A4) enzymes, it can reduce the plasma levels of the anti-HIV protease inhibitor³⁶⁶³ indinavir, warfarin, theophylline, and cyclosporin. (see Mills ea, 2004) Interactions between SJW and cyclosporin may lead to transplant rejection. Oral contraceptive efficacy may be diminished by SJW. Woelk (2000) compared SJW with relatively modest doses of imipramine (150 mgs. /day) in a randomised, multicentre, double blind, parallel group study involving mild to moderate outpatient depressives.

Kennedy (2010) suggested that M1 agonism leads to circadian phase advance and resynchronisation of disrupted rhythms whereas M2 agonism affects prefrontal DA and norepinephrine release by blocking the inhibitory action of GABA. He stated that agomelatine promotes neurogenesis by increasing cell proliferation and aiding cell survival in the ventral dentate gyrus. DA release in the accumbens is unaffected. Glutamate release may be reduced. Transcription factors and BDNF are increased. There is evidence for acute and sustained antidepressant activity. It reduces symptoms of GAD. Dizziness was the adverse effect that separated best from placebo. ALAT and ASAT liver enzymes may rise reversibly but Kennedy does not view agomelatine as a hepatotoxic drug. It appears to be weight neutral. It has a better sexual function profile than venlafaxine and is non-sedating and has no appreciable effect on GIT function, blood pressure, heart rate or QTc.

³⁶⁵⁸ Leonard (2007) suggested that the main effect is antagonism of 5-HT₂ receptors and questions the relevance of its effects on melatonin receptors. Agomelatine does not suppress REM sleep.

³⁶⁵⁹ Blockade of 5-HT_{2C} receptors is thought to enhance fronto-cortical dopaminergic and adrenergic pathway activity. (Millan ea, 2003)

³⁶⁶⁰ This was confirmed by other analyses and criteria: responders, remission, sub-population of severely depressed patients,

Montgomery-Asberg Depression Rating Scale, Clinical Global Impression-Severity of Illness.

³⁶⁶¹ SJW (*Wort, Rose of Sharon, goat weed, Klamath weed*: herb or vegetable), or extracts of the plant *Hypericum perforatum*, is of ancient vintage. It was used in classical times as a diuretic and as an aid to wound-healing. It received its name from the story that it grew from ground upon which the blood of John the Baptist fell when he was beheaded. An alternative story is that it blooms on June 24th, the traditional birthday of John the Baptist. It can cause a rash in humans and in goats and sheep.

³⁶⁶² The serotonergic effects of SJW are weak.

³⁶⁶³ Carbamazepine can render protease inhibitors less effective.

Both preparations were equally effective although SJW was better tolerated. This study cannot answer the question as to whether an inert placebo would have performed as well under the circumstances. Shelton *et al.* (2001) and Lecrubier *et al.* (2002) found it ineffective and effective for major depression respectively, a contradiction reflected in a meta-analysis of RCTs. (Linde *et al.*, 2005)

Other antidepressants

Mianserin (e.g. Tolvon³⁶⁶⁴) is a sedative tetracyclic that inhibits presynaptic α -2 receptors and thereby 'fools' the cell into liberating extra neurotransmitter. It can cause blood dyscrasias in 1:4,000 treated patients³⁶⁶⁵, and therefore, monthly blood counts have been advised, at least during the initial period of treatment. Mianserin is relatively safe in overdose. Girard (1988) believes that hepatotoxicity from mianserin is not a significant problem. Mianserin has been recommended for the treatment of depression in cancer patients. (Van Heeringen & Zivkov, 1996)

Trazodone (Molipaxin), a sedative triazolopyridine more often employed as a sedative-hypnotic, can rarely cause priapism (1 in 6,000 males treated³⁶⁶⁶) or arrhythmias in those patients with heart disease (pre-existing premature ventricular contractions or mitral valve prolapse). According to the APA (2002, p. 500) the evidence for trazodone's arrhythmogenicity is anecdotal only. Trazodone increases slow wave and total sleep time and has little or no effect on REM sleep. (Yamadera *et al.*, 1998) Trazodone is a mixed 5-HT agonist-antagonist. Its active metabolite, m-chlorophenylpiperazine (m-CPP), is a potent direct serotonin agonist. Trazodone is available in capsular, tablet and liquid (50 mg/5 ml) form. It has a half-life of 3-9 hours. It is often used to manage insomnia during early SSRI or bupropion treatment, but use as an antidepressant is reduced by the need for multiple daily doses and sedation. Avoid trazodone with MAOIs. Side effects include sedation (in low doses it is a useful hypnotic – may cause daytime drowsiness), orthostatic hypotension, dizziness, headache, nausea, and gastric irritation. It can occasionally cause dry mouth via α -1-adrenergic blockade. There is some risk of GIT bleeding. (Po, 1999) Spontaneous orgasms in a postmenopausal woman on trazodone have been reported. It has minimal anticholinergic side effects and it may be less epileptogenic than the TCAs. Delirium has been reported in bulimic patients taking trazodone. Trazodone may have a role in the control of screaming in the disturbed elderly. (Craig & Burns, 2000) Trazodone does not appear to have a withdrawal syndrome.

L-tryptophan, the amino precursor of the brain amine serotonin, may potentiate the antidepressant properties of some antidepressants such as MAOIs or TCAs (with some risk of a serotonin syndrome if given with these or SSRIs). It is formulated with and without added vitamins (Pacitron, Optimax), the latter being added in the hope of promoting 5-HT synthesis, or to prevent its breakdown by hepatic enzymes. There are conflicting reports about its efficacy. Warm milk contains sufficient L-tryptophan to account for its historical use as a soporific: carbohydrates (cookies) increase L-tryptophan absorption. L-tryptophan has been associated with an eosinophilia-myalgia syndrome with an increase in white blood cells ($> 2,000$ eosinophils/ml), joint pains, swelling of the arms and legs, skin rash/scleroderma³⁶⁶⁷, and pyrexia. The eosinophilia-

³⁶⁶⁴ Removed from market 2006.

³⁶⁶⁵ Chlorpromazine probably causes more haematological problems than does mianserin.

³⁶⁶⁶ Clitoral priapism is very rare. (Pescatori *et al.*, 1993)

³⁶⁶⁷ Resembling scleroderma.

myalgia syndrome³⁶⁶⁸ can continue to evolve even after withdrawal of the drug. L-tryptophan is available on a named patient basis only.

Doxepin (Sinequan), a CPY 2D6 inhibitor and the most potent antihistamine in clinical medicine (FDA approved for treatment of anxiety), is sometimes used topically as treatment for pruritus. It is to be withdrawn from the Irish market as of end November 2006 because 'the production site is no longer in operation'. (Pfizer, letter dated January 9, 2006)

Maprotiline (Ludiomil) is a 'tetracyclic' or modified TCA³⁶⁶⁹ that selectively inhibits noradrenaline re-uptake. Its formula resembles that of nortriptyline and its side effect spectrum is very similar to the TCAs. It can cause rashes and is epileptogenic. (Schmidt et al, 1986) It can also be cardiotoxic. (Howland & Thase, 2002)

Flupenthixol (flupentixol: Fluanxol) in a low dose oral preparation may have some antidepressant effect (Young et al, 1976), possibly because of blockade of presynaptic autoreceptors (the same could be said of thioridazine).

Alprazolam (Xanax, Calmax), a BZD, is of benefit in minor neurotic depressions with associated anxiety. It has been used in high doses for panic disorder.

Liothyronine (triiodothyronine or T3) has been used to accelerate the antidepressant action of TCAs. Anginal exacerbation and paroxysmal atrial fibrillation have been reported in elderly patients. (e.g. Cole et al, 1993)

Oestrogens increase plasma TCA levels by inhibiting their metabolism.

Minaprine, an amino-phenylpyridazine, has little anticholinergic, cardiotoxic, sedative, or weight promoting properties. (Wheatley, 1992)

S-adenosylmethionine, a methyl donor, may have antidepressant activity. It can cause nervousness, insomnia, headache and mild GIT upset.

Bupropion (Zyban, Wellbutrin) can cause seizures in higher doses³⁶⁷⁰ and the commonest side effect is excessive stimulation. Psychotic symptoms can occur (Howard & Warnock, 1999) and derive from *dopaminergic* stimulation³⁶⁷¹. If added to L-DOPA there is the potential for hallucinations, confusion, and dyskinesia. Metabolites of bupropion may yield false-positive results for amphetamine in urine as the chemical structure of this unicyclic drug³⁶⁷² resembles that of amphetamine. Bupropion, used in low dosage, may attenuate the sexual dysfunction caused by other medication. Its dopaminergic effects account for its use (in lower doses than for depression: Leonard, 2007) as an aid in smoking cessation. Bupropion is also used to treat ADHD. There does not appear to be a bupropion withdrawal syndrome.

Resistant depression

The occasional depressive does not respond to any of the above drugs. The diagnosis should be reviewed and any missed clue sought, such as social or personality difficulties. The drug may not have been given in optimal dosage or taken at all. Combinations of drugs may be tried. Augmentation strategies may be used. T3 (5-50 mcg) may be superior to T4 in converting TCA non-responders to responders. ECT, sleep deprivation, behaviour or cognitive therapy are other approaches to treatment. Psychosurgery is a very last resort.

Continuation therapy

Mindham et al (1973) evaluated continuation therapy with TCAs in depressives. It was a multi-centre double blind trial conducted throughout Great Britain. The trial was

³⁶⁶⁸ The most likely explanation seems to be that a change in the production process (less powdered carbon) in a Tokyo company led to contamination with strain V of *Bacillus amyloliquefaciens*. A similar syndrome, toxic oil syndrome, followed ingestion of contaminated olive oil.

³⁶⁶⁹ 6-membered central ring stabilised by an ethylene bridge.

³⁶⁷⁰ Particularly in patients with **bulimia nervosa** or a **history of head injury**. The metabolites of bupropion are excreted by the kidney. In patients with end-stage renal disease these metabolites may accumulate and cause seizures.

³⁶⁷¹ There is a structural relationship to amphetamine.

³⁶⁷² A monocyclic phenylbutamine of the aminoketone type.

designed to assess a six-month course of continuation (syn. maintenance) therapy to see if it would prevent a recurrence of symptoms in those patients successfully treated with either imipramine or amitriptyline. Ninety-two patients entered and significantly fewer on active therapy relapsed during the six months: 22% compared with 50% of those on placebo. An interesting finding was that more people complained of dry mouths than could be attributed to the active drugs.

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29

Antipsychotic and anticholinergic drugs

Brian O'Shea

'The spasmodic phenomena of the face and of speech which often appear are extremely peculiar disorders...' (Kraepelin, 1919)

'...in the ideal situation one searches for a gold standard which has virtually no side effects. However, such drugs do not exist.' (Ellenbroek & Cools, 2002)

'We don't wait long enough for a drug to work: time is a drug.' (Stahl, 2003)

'The better someone is doing, the more they have to lose if they stop their medication.' (Kane, 2003)

Antipsychotic drugs³⁶⁷³ ameliorate psychotic symptoms such as hallucinations, thought disorder and delusions, irrespective of underlying cause. (O'Shea, 1998) They are much less efficacious for schizophrenic negative symptoms³⁶⁷⁴. They produce unpleasant feeling states in normal subjects (and 'negative symptoms': Artaloytia ea, 2006) and are therefore of very low abuse potential. Antipsychotic drugs all block postsynaptic dopamine (DA) receptors to a variable extent. Promazine and mepazine have little or no antipsychotic activity. Very high doses of antipsychotic drugs, once commonly employed, should only be resorted to as a last resort. (Hirsch & Barnes, 1994) Use of multiple antipsychotic drugs may increase adverse events and time spent in hospital but with no added clinical benefit. (Centorrino ea, 2004) Koreen ea (1994) gave oral fluphenazine to psychotic patients and found no difference between plasma levels between responders and non-responders and no correlation with measures of psychopathology or extrapyramidal symptoms (EPS). Plasma levels of chlorpromazine³⁶⁷⁵ correlate poorly with therapeutic effect and better with prolactin secretion. However, according to Volavka ea, (1995) plasma levels of haloperidol³⁶⁷⁶ up to c 12 ng/ml may correlate with antipsychotic effect for the first few months (5-20 ng/ml according to other authors), whereas a lower level may improve negative symptoms thereafter. Patients may show large changes in plasma clozapine levels without any change in psychopathology – there is no need to adjust dose if these patients show plasma level variations of +/- 50%. However, larger changes might suggest compliance difficulties. (Kurz ea, 1998) Antipsychotic drugs may give a false-positive pregnancy test. (Edwards, 1995)

Leptin is produced by fat cells and may provide feedback to the brain on the size of adipose tissue. Patients on clozapine or olanzapine may experience a significant increase in weight, BMI and circulating leptin levels, whereas these measures remain stable in subjects on haloperidol or no medication. This may mean that there is reduced feedback of leptin to the CNS, or it could simply mean overeating. (Kraus ea, 1999) Weight gain with, say olanzapine, might be due to its antihistaminic (H1), D2 or 5-HT2C³⁶⁷⁷

³⁶⁷³ Formerly 'neuroleptics' or 'anti-schizophrenic' drugs.

³⁶⁷⁴ E.g. anergia, anhedonia, etc.

³⁶⁷⁵ 3-(2-chloro-10H-phenothiazin-10-yl)-N,N-dimethyl-propan-1-amine. Phenothiazine dyes were developed for commercial use in the 1880s and chlorpromazine is a derivative of such compounds.

³⁶⁷⁶ 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one.

³⁶⁷⁷ 5-HT2C knockout mice become obese. The presence of a T allele in the promoter region of the 5-HT2C receptor gene may be associated with lessened propensity for antipsychotic-induced weight gain. Also, the 2548GG genotype at the leptin gene increased

antagonism. Clozapine, in terms of weight gain is the main offender³⁶⁷⁸, followed in descending order by olanzapine, sertindole, risperidone, and ziprasidone. However, haloperidol may be associated with slower (over a year) and equally significant weight gain.(Perez-Iglesias ea, 2008)

Antipsychotic drugs may activate lipid homeostasis genes, at least in vitro (Polymeropoulos ea, 2009), and they may alter the ratio of polyunsaturated to saturated fatty acids and cholesterol content.

Side effect profile in a 90-day Pakistani study of three antipsychotic drugs³⁶⁷⁹

	Body weight Kg (ante/post)	Prolactin ng/dl (ante/post)	Glucose mg/dl (ante/post)
Olanzapine	70.1/72.4*	14/14.9*	123.3/166.6*
Risperidone	69.70.7*	16/49.3*	114.9/118
Quetiapine	64.7/65.4*	12.6/13.5*	114.4/115

*P<0.05 for inter-group comparisons

Among conventional (typical) drugs, the situation varies from weight reduction with molindone³⁶⁸⁰ and loxapine to weight gain with thioridazine. Zipursky ea (2005) found significant weight gain in patients treated with olanzapine or haloperidol. A study by Zhang ea (2004) showed significant increases in subcutaneous and intra-abdominal fat (on MRI), a three-fold increase in leptin secretion, and significant increases in levels of circulating lipids and non-fasting glucose in patients treated according to normal local clinical practice (risperidone or chlorpromazine). Weight and blood glucose monitoring of in-patients is the exception rather than the rule.(Boilson & Hamilton, 2003)

Antipsychotic drugs that raise prolactin levels (incl. reserpine: Perkins, 2003, p. 220) should not be used in the presence of a pituitary prolactinoma or breast cancer. No drug of any type to which a patient has shown hypersensitivity should be given to such a patient. The manufacturer's latest data sheet should be consulted when in doubt over dosage schedules or other critical information. In reality, atypical drugs can raise prolactin levels but differ in degree and duration of dose-dependent prolactin elevation (risperidone > olanzapine or clozapine) due to differential binding properties of each drug on pituitary D2 receptors.(Turrone ea, 2002) Abraham ea (2003) found no acceleration of bone mineral density loss due to increased prolactin levels in females on risperidone or olanzapine for one year; perhaps higher prolactin levels over a longer time span might have had an effect. However, Meaney ea (2004) found reduced mineral density in schizophrenic subjects on longterm prolactin-raising antipsychotic drugs and lower testosterone levels in men was associated with reduced bone mineral density; but the study contained no comparison group and the females were past the menopause so that associations with gonadal status could not be measured. Burt and Hendrick (2003, p. 1527) suggest the following approach to managing raised prolactin levels (normal range = 5 – 26 ng/ml): consider reducing the dose of the antipsychotic drug; try dopamine agonist (bromocriptine, 2.5 – 7.5 mg b.i.d. or cabergoline 0.5 mg weekly); or use an oral anovulant. Amenorrhoea usually occurs with prolactin levels over 60 ng/ml. If the level exceeds 100 ng/ml, consider endocrinological referral to outrule a pituitary adenoma.

BMI in schizophrenic patients given antipsychotics.(Reynolds, 2009 – see also Reynolds, ea, 2003) Increases in body fat leads to raised **leptin** levels that then signal the brain to cease food intake. However, antipsychotics, by blocking hypothalamic receptors, interfere with this message from circulating leptin.

³⁶⁷⁸ At least in males, the presence of the -759T variant allele of the **5-HT2C** gene may protect against significant weight gain with clozapine.(Reynolds ea, 2003) There is evidence that weight gain associated with atypical drugs may result to some extent due to predisposition as shown by a study (Gebhardt ea, 2009) looking at clozapine, olanzapine and risperidone where predictors of increased weight were increased parental BMI, patients' premorbid BMI, female sex, younger age and (as a trend) diagnosis of schizophrenia spectrum disorder.

³⁶⁷⁹ Chaudhry ea.(2008) Drug-naive schizophrenia cases; random assignment; only lorazepam allowed; 40 cases each per drug; means only.

³⁶⁸⁰ Molindone (Moban) is unlikely to significantly increase vulnerability to seizures.

Typical antipsychotic drugs

Chlorpromazine (CPZ³⁶⁸¹) is partially absorbed from GIT, less so in the presence of an antacid. It reaches peak serum levels 2-4 hours after oral ingestion³⁶⁸². IM injections produce 4-10 times higher plasma levels than occurs with the same dose given orally because first-pass metabolism is avoided, the drug avoiding the liver and gaining direct access to the systemic circulation. IV injections of CPZ are best avoided because of the danger of precipitating cardiac arrhythmias. IM injections of CPZ have become much less acceptable since the 1990s because of the potential for cardiovascular adverse effects, including severe postural hypotension. 95% of CPZ is bound to plasma proteins. CPZ is metabolised by gut wall and liver. The 7-hydroxy derivative has therapeutic properties but the sulphoxide is inactive.

Dopamine (DA)

DA inhibits prolactin release

Most antipsychotic drugs inhibit DA causing hyperprolactinaemia +/- galactorrhoea

Bromocriptine is used to treat galactorrhoea

Amenorrhoea is due to negative feedback on the brain by prolactin causing decreased gonadotrophin release

Phenothiazines compete for the same enzymes as do TCAs, and either will prolong the activity of the other³⁶⁸³

Apomorphine is a direct, partial DA agonist that stimulates DA autoreceptors when given in small doses

Peripheral oedema

Occurs in 1-3% of patients on phenothiazines and other psychotropics with prominent antidopaminergic activity

Dopaminergic neurones enhance sodium excretion by direct effect on renal tubule and by modulating renin and aldosterone secretion

Consider antipsychotic drugs in differential diagnosis of idiopathic oedema

After a wave of depolarisation, calcium and sodium move via ion channels into the neurone. This has a series of effects leading to the opening of other channels through which potassium ions move out of the cell. Sulpiride will decrease hyperpolarisation as an acute neuroleptic defect, but with chronic application of a neuroleptic rebound hyperpolarisation occurs. Rebound over activation of such systems roughly parallels clinical improvement after days to weeks, and the net effect is that such neurones (in the rat) become less sensitive to environmental stimulation.³⁶⁸⁴ Blockade of D2 receptors is thought to provide the therapeutic effect of typical antipsychotic drugs³⁶⁸⁵. Blockade of alpha-1 adrenoreceptors may provide the sedative effect.(see table) The tendency of neuroleptics to cause extrapyramidal side effects varies inversely with their muscarinic cholinergic antagonistic potency. The EEG of patients on antipsychotic drugs shows

³⁶⁸¹ Largactil (4560 RP, synthesised from phenothiazine antihistamines in 1950 by Paul Chapentier of Rhône-Poulenc: Turner, 2007) withdrawn 2005; still available from Clonmel Laboratories as Clonazine.

³⁶⁸² Tobacco smoking significantly increases the dose of neuroleptic needed in schizophrenia, but is associated with a significant reduction in levels of Parkinsonism(Goff ea, 1992); reduced and raised serum clozapine levels while smoking and on smoking cessation respectively (smoking cessation may lead to sedation, etc. from clozapine); tobacco induces cytochrome enzymes such as CYP1A2.

³⁶⁸³ Accepting that there will be individual variations, the following are the mean times (in hours) for peak concentration in the blood and biological half-lives (respectively, in brackets) of a sample of oral antipsychotic drugs - chlorpromazine (2-4; 30), fluphenazine (2; 16), flupenthixol (4;35), cis (Z) - clopenthixol (4;20), haloperidol (5;20 - a relative of pethidine; discovered by Paul Janssen), perphenazine (2-4; 9), and pimozide (8;54).

³⁶⁸⁴ This may be in keeping with Broadbent's theories (Broadbent, 1971) on the filter abnormalities in schizophrenia whereby schizophrenics cannot keep irrelevant environmental stimuli out of consciousness and thereby become hallucinated and deluded, eventually withdrawing from society to ward off stimulation.

³⁶⁸⁵ According to PET studies of haloperidol D2 occupancy varies from 38% to 87% and the degree of occupancy predicts clinical improvement, hyperprolactinaemia and EPS. However, some studies suggest that optimal doses of low-potency conventional antipsychotics may not induce more EPS than atypical drugs.(Leucht ea, 2003)

increased synchronisation and voltage and less effect of incoming sensory information on alpha rhythm. Centorrino et al (2002) found the frequency of EEG abnormality to be high with clozapine and olanzapine, moderate with risperidone and typical agents, and low with quetiapine; comorbid hypertension, bipolarity, and older age, but not dose or clinical response, were associated with such abnormalities.

*Some assumed clinical correlates of blockade of receptors by antipsychotic drugs*³⁶⁸⁶

<i>Receptor</i>	<i>Effects</i>
Dopaminergic	EPS (D2 in basal ganglia), NMS, reduced drive, increased prolactin, weight gain
Muscarinic (Ach)	cycloplegia, dry mouth, memory problems, reflex tachycardia, constipation, urinary retention (latter may respond to bethanechol [Urecholine] 15 mg tid)
Histamine (H1)	sedation, drowsiness, potentiation of central depressant drugs, weight gain, postural hypotension
Noradrenergic	tachycardia, inhibition of ejaculation (alpha-1-antagonism, esp. piperidine phenothiazines like thioridazine and mesoridazine), tremor, augmentation of pressor effects of noradrenaline
Alpha-1-adrenergic	dizziness, postural hypotension, reflex tachycardia, impotence
5-HT1A	weight gain
5-HT2	less Parkinsonism and dystonia

Carbamazepine is a potent inhibitor of liver enzymes and lowers the blood levels of haloperidol, which could potentially worsen the symptoms of a schizophrenic. Methyldopa can greatly increase blood levels of haloperidol.

The beneficial effect of active antipsychotic drugs develops over several weeks. Positive schizophrenic symptoms show most drug-related improvement during the third week of treatment; improved social functioning continues to develop for several months if drug treatment is combined with occupational therapy in a milieu appropriate to the patient's abilities.

One action of oxypertine³⁶⁸⁷ is a reserpine-like depletion of neuronal transmitters. Post-synaptic D2 receptor agonists, such as bromocriptine, can potentially precipitate a psychosis, even in persons without a prior history.

Secondary negative symptoms, such as mutism and social withdrawal secondary to positive psychotic phenomena³⁶⁸⁸, tend to improve with treatment.³⁶⁸⁹

³⁶⁸⁶ PET studies show antipsychotic drugs block D2 receptors in mesocortical and mesolimbic dopaminergic pathways almost immediately. However, antipsychotic effects require weeks to develop. Also, clozapine has weak affinity for D2 receptors. Also, most antipsychotics have active metabolites with half-lives longer than the parent compounds, so relapse may be delayed for months in some cases after the drug is stopped. The presence of active metabolites and the accumulation of drug in adipose tissue have made it impossible to produce a reliable dose-response curve for neuroleptics.

IV haloperidol has been noted to cause less EPS than oral haloperidol. There is a small risk of *torsades de pointes* ('twisting of the points': described in 1966, a polymorphic arrhythmia [rapid irregular complexes oscillate around baseline] causing syncope and death, associated with prolonged QT, tendency to not benefit from antiarrhythmic drugs, congenital and drug-induced forms; hypokalaemia and hypomagnesaemia may predispose to arrhythmias). For example, 4 cases of *torsades de pointes* were recorded as being due to IV haloperidol among 1,100 consecutive patients in an ICU. (Wilt et al, 1993) Haloperidol is changed to reduced haloperidol in the liver. IV haloperidol enters the CNS before metabolites are produced. This has led to the suggestion that blockade of D2 receptor by haloperidol rather than reduced haloperidol might be responsible for EPS. Phenytoin and heparin precipitate haloperidol, so flush IV tubing with normal saline before giving haloperidol if either of these agents have been used. The Massachusetts General Hospital (Murray, 1991) suggests the following protocol for IV haloperidol in the control of agitation in delirious or demented patients: initially, for mild/moderate/severe agitation give (in mg.) 0.5-2/5-10/10 or more; if still agitated after 20 minutes, double the initial dose; repeat last step until control is achieved. Tachycardia from antipsychotic medication may arise from anticholinergic or postural hypotensive actions.

³⁶⁸⁷ Withdrawn in 1999.

The combination of CPZ and cimetidine may lead to excessive sedation. If the CPZ dose is then reduced and the cimetidine eventually withdrawn the schizophrenic symptoms may get worse, necessitating an increase in the dose of CPZ. (Byrne and O'Shea, 1989). Beta-Blocking drugs increase antipsychotic drug levels.

Oral medication in schizophrenia has certain advantages and disadvantages. Amongst the advantages are a short duration of action and an increased flexibility of dose in the short term. Amongst the disadvantages poor compliance and possible overdose.

The main groups of antipsychotic drugs are shown in the table. Phenothiazines have a three-ring nucleus and members of the family differing in the side chains that are joined to the N atom in the middle ring. The depots available for use, with the exception of fluspiriline (an aqueous suspension), are esters (-COOH) of an active neuroleptic drug plus a long chain fatty acid. The neuroleptic-fatty acid ester is dissolved in an oil vehicle and given by deep IM injection. The ester is released from the oil phase by slow diffusion into the body water phase. Direct or indirect evidence of depot antipsychotic drugs can be found in the body up to 6 months after administration of the drug was stopped. (Wistedt ea, 1981) Local reactions to depots can be reduced in frequency by the use of lower volumes (concentrates), a lower injection frequency, and by ensuring deep intramuscular (rather than subcutaneous) delivery.

Classification of antipsychotic drugs

Phenothiazines: (a) aliphatic, e.g. CPZ (particularly epileptogenic), levopromazine, trifluopromazine
 (b) piperidine, e.g. thioridazine (Melleril, Melzine, Thiozine, etc), mesoridazine, pericyazine
 (c) piperazine, e.g. trifluoperazine (Stelazine), fluphenazine decanoate (e.g. Modecate, formerly Anatensol; Prolixin in USA), prochlorperazine, perphenazine
 Butyrophenones, e.g. haloperidol (Serenace, Haldol – developed by Paul Janssen from pethidine in late 1950s), droperidol³⁶⁹⁰, benperidol, trifluoperidol
 Thioxanthines (synthesised in Denmark by Petersen and co-workers in the late 1950s), e.g. flupenthixol (flupentixol) decanoate (Depixol), clopenthixol decanoate (Clopixol), chlorprothixene, thiothixene; thioxanthines can be (a) aliphatic or (b) piperazine
 Dihydroindolones, e.g. molindone (Moban), oxypertine
 Diphenylbutylpiperidines, e.g. pimozide (Orap), fluspiriline
 Substituted benzamides, e.g. sulpiride (Dolmatil), amilsulpride (Solian), raclopride, remoxipride³⁶⁹¹
 Dibenzothiazepine, e.g. quetiapine (Seroquel)
 Dihydroindolones, e.g. molindone
 Benzisoxazoles, e.g. risperidone (Risperdal), iloperidone (Zomaril)
 Dibenzodiazepines, e.g. clozapine (Clozaril)
 Dibenzoxazepines, e.g. loxapine (Loxitane)
 Thienobenzodiazepines, e.g. olanzapine (Zyprexa)
 Benzothiazolylpiperazine, e.g. ziprasidone HCl (Geodon)
 Rauwolfia alkaloids, e.g. reserpine
 Quinolinone, e.g. aripiprazole (Abilify)
 Phenylindol, e.g. sertindole (Serdolect)
 Dibenzothiepine, e.g. zotepine

Depot antipsychotics include:

³⁶⁸⁸ Causing the patient to be preoccupied with delusions and hallucinations.

³⁶⁸⁹ It should be noted that negative symptoms may occur with temporal lobe epilepsy. (Getz ea, 2002)

³⁶⁹⁰ Droperidol (Droleptan) is a systemically administered butyrophenone with a short duration of action and may need to be given repeatedly. It is a potent alpha-adrenergic receptor antagonist that causes less hypotension than CPZ. It has very little affinity for central histamine receptors, which may account for its relatively weak sedative effect. The main uses of droperidol were its use in conjunction with narcotic analgesics in neuroleptanalgesia; as a premedication alone or with a narcotic analgesic; and in the acute management of the agitated manic patient. Because of concerns raised about prolongation of the QT interval, droperidol was withdrawn from the market in 2001. It was also associated with frightening dreams.

³⁶⁹¹ Remoxipride (Roxiam), a substituted benzamide and selective D2-receptor antagonist, was withdrawn in 1994 because of associated aplastic anaemia. Sertindole (Serdolect), an atypical drug, was also removed from the market in 1998, this time because of QT prolongation. (O'Shea, 1998) only to reappear again in 2007.

Flupenthixol (flupentixol: Depixol) 20 mg test dose, 1-4 weekly injections.

Zuclopenthixol (Clopixol) 50 mg test dose, 1-4 weekly injections; zuclopenthixol acetate solution (5%) or Clopixol Acuphase (50-150 mg – suggested max dose 400 mg in 4 injections) is useful for rapid control of psychotic behaviour and lasts 2-3 days after deep IM injection. Longer-lasting depot neuroleptics can and have been started simultaneously with zuclopenthixol acetate.

Haloperidol decanoate (Haldol Decanoas) 25 mg test dose, 4 weekly injections.

Fluphenazine decanoate (Modecate) 12.5-20 mg test dose, 1-4 weekly injections.

Fluphenazine HCL (Moditen Enanthate).

Pipothiazine palmitate (Piportil - withdrawn 2007).

Fluspiriline (Redeptin, a phenylbutyl piperidine) 2 mg test dose, weekly injections (may get local fibrotic nodules).

Olanzapine (Zyprexa IM) see below under atypical drugs.

Olanzapine palmoate (Zypadhera)

Risperidone depot - see below under atypical drugs.

Ziprasidone mesylate IM lasts for 3 days.

Thioridazine (Melleril, Melzine, Thiozine), which is (unlike trifluoperazine and the butyrophenones) strongly anticholinergic, may prolong the QT interval (blockade of delayed rectifier potassium channel {I(Kr)} leading to prolonged cardiac repolarisation). Use is now restricted to second line treatment of adult cases of schizophrenia under the supervision of a consultant psychiatrist. Contraindications include a history of 'clinically significant' cardiac disorders including arrhythmias, conduction disorders or a history of QTc prolongation (> 450 msec, although > 500 msec seems more realistic and it should be noted that the mean QTc varies in individuals by 76 msec each day). Other conditions/medicines that lead to electrolyte imbalance may increase the risk for serious cardiac arrhythmias. It is 'recommended' that patients have electrolyte estimations and an ECG before and periodically during thioridazine administration. As of December 2000, Novartis limited the use of thioridazine (Melleril) to adult schizophrenia under the supervision of a consultant psychiatrist. Possible mechanisms of sudden death in neuroleptic-treated patients include (a) unrelated, (b) cell membrane sodium pump blockade, (c) NMS, (d) CNS/respiratory depression, (e) hypoxaemia, (f) seizures, and (g) hypotension.(O'Shea, 1998) In the case of thioridazine, mutated genes coding for CYP2D6 isoenzyme (debrisoquine hydroxylase) may lead to metabolite accumulation and potential cardiotoxic effects.(Reilly ea, 2002) Mutations at the HERG (human 'ether-a-go-go') locus causes a congenital long QT syndrome in which potassium channel current is reduced and torsade de pointes occurs frequently, and arrhythmias become more likely following further blockade by drugs. It has also been surmised that the chief reason for cardiac and ejaculatory side effects of thioridazine lies in calcium ion channel blockade – ECG changes produced by thioridazine resemble those caused by verapamil. Mesoridazine (Serentil), a major metabolite of thioridazine, can prolong the QTc interval. Pimozide (Orap), a potent calcium antagonist with a half-life of 53 hours on average, should be avoided in patients with long QT intervals or in patients on drugs that prolong that interval (like TCAs). Regular ECGs, a slow increase in dose, and a low final dose may obviate problems. Also, seizures may occur with high-dose pimozide. This subject is discussed further under the heading 'sudden death' below. The combination of pimozide and fluoxetine can lead to bradycardia and/or delirium. Do not combine pimozide and other calcium channel blocking drugs, such as nifedipine, diltiazem, and verapamil. Drugs that inhibit P450 3A4 enzymes (e.g. erythromycin and nefazodone) increase pimozide levels. Atypical antipsychotic drugs may carry similar risk for sudden death as do the typical (older) drugs.(Ray ea, 2009)

Antipsychotic drugs are **contraindicated** in myasthenia gravis, Addison's disease, narrow angle glaucoma (lase with ophthalmologist), and past or present bone marrow suppression. Special caution is required in cases with renal disease, cardiovascular disorder, Parkinsonism, epilepsy, and serious infection.

Irish Medicines Board (2007) summary of EU review conclusions

Do not use *haloperidol*, *pimozide*, *sertindole*, or *ziprasidone* if there is

- Clinically significant heart disorder (recent MI, uncompensated heart failure, arrhythmias treated with class 1A³⁶⁹² and III anti-arrhythmic drugs)
- QTc prolongation
- History of ventricular arrhythmia or *torsades de pointes*
- Uncorrected hypokalaemia³⁶⁹³
- Patient on another QT interval-prolonging drug

Use these drugs with caution if there is cardiovascular disease or a family history of long QT.(Roden, 2008) Do baseline ECG and consider need for ongoing ECG monitoring. Decrease dose if QT lengthens and discontinue if > 500 ms. Monitor electrolytes and avoid other neuroleptics.

³⁶⁹² Tricyclic antidepressants have class 1A antiarrhythmic properties.

³⁶⁹³ Low magnesium is also a risk factor for prolongation of the QTc interval, as is use of cocaine.

With other antipsychotic drugs exercise caution in cases of cardiovascular disease or family history of long QT, and avoid concomitant use of other neuroleptics.

Drugs such as trifluoperazine and haloperidol are capable of causing stronger EPS than, say, thioridazine³⁶⁹⁴. Antiparkinsonian drugs should be avoided where possible (e.g. lower dose of CPZ) or given only for a brief period. It has been suggested that prolonged use in combination with antipsychotic drugs increase the likelihood of developing tardive dyskinesia (TD). Prochlorperazine (Stemetil) has little or no antipsychotic actions and is mainly used as a sedative or antiemetic. Perphenazine (Fentazin) and pericyazine (Neulactil) are less sedative than CPZ.

CPZ has many non-psychiatric uses, e.g. hiccough³⁶⁹⁵, antiemetic, coolant³⁶⁹⁶, etc. Sulpride (Dolmatil) is a substituted benzamide. In low doses (200-400 mgs BID) the greater affinity of the drug for the presynaptic receptors blocks negative feedback to the presynaptic neurone and the resultant increase in DA in the synaptic cleft may have an alerting effect. With higher doses (400-1,200 mgs BID), both pre- and postsynaptic receptors are blocked, giving a neuroleptic-type effect. Furthermore, postsynaptic D2 receptors (implicated in schizophrenia) are blocked, whereas D1 receptors function normally. The maximum recommended dose is 2,400 mgs per 24 hours. The idea is to use low doses for 'negative' symptoms and higher doses for 'positive' symptoms. Loxapine (Loxapac), a tricyclic dibenzoxazepine like amoxapine with some structural similarity to phenothiazines and carbamazepine, is started at 20-50 mg/day in two doses. It is increased over 7-10 days to 60-100 mg/day, given twice to four times per day. The usual maintenance dose is 20-100 mg/day, and the maximum daily dose is 250 mgs. The elimination half-life is 7 hours. It has the usual range of adverse effects, including TD. According to Buckley and McManus,(1998) loxapine had the highest fatal toxicity index (deaths due to poisoning) of all antipsychotics. Fits³⁶⁹⁷ can occur with overdose of this drug. Loxapine has been shown to be as effective as haloperidol in acute schizophrenia with less potential to cause EPS.

Adverse effects of antipsychotic drugs (O'Shea, 1998)

Skin - allergic reactions, photosensitivity dermatitis³⁶⁹⁸, hair loss³⁶⁹⁹, pigmentary changes³⁷⁰⁰ in skin and cornea, opaque lens

Blood - transient rise or fall in WCC (benign leucopaenia in up to 10% on CPZ: Kane ea, 1992), eosinophilia, agranulocytosis,³⁷⁰¹ and idiopathic venous thromboembolism³⁷⁰²

Liver - transient elevation of enzymes, and cholestatic jaundice; avoid CPZ in presence of liver disease

³⁶⁹⁴ There may be an individual propensity to EPS as there is a tendency for the same patients to develop them on successive exposures to neuroleptic drugs.(Keepers & Casey, 1991)

³⁶⁹⁵ Haloperidol, metoclopramide, carbamazepine, valproic acid, phenytoin, perphenazine and baclofen are other treatments for persistent hiccough.(Howard, 1992)

³⁶⁹⁶ During the early years of heart surgery.

³⁶⁹⁷ These are probably due to potent GABA_A receptor antagonism.

³⁶⁹⁸ Use a strong sunscreen factor or Uvistat.

³⁶⁹⁹ Usually increased shedding, rarely different degrees of alopecia; less common than with TCAs and mood stabilisers.(Warnock, 1991)

³⁷⁰⁰ Pigmentation of the gums may be caused by many substances, e.g. phenothiazines, anti-malaria drugs, lead, mercury, and bismuth.

³⁷⁰¹ 0.32% with CPZ.(Kane ea, 1992) If there is persistent sore throat or fever stop the drug and check WCC. Clozapine may cause a benign fever that responds to paracetamol.

³⁷⁰² This was thought to be more likely in patients on typical agents, especially low potency ones, but atypical agents are not devoid of this risk.(Hägg & Spigset, 2002; Selten & Büller, 2003; Waage & Gedde-Dahl, 2003; Hilli ea, 2008; Srihari & Lee, 2008; Gunasekaran, 2010) Possible mechanisms include venous stasis due to sedation, increased platelet aggregation, anti-cardiolipin action, or antibodies.

Cardiac - wide, flat T waves, increase in QT interval (sudden death is thought to be rare), (haloperidol is relatively safe in this regard), thioridazine may reverse inotropic effect of digitalis (quinidine-like effect)

Metabolic³⁷⁰³/**Endocrine** - weight gain,³⁷⁰⁴ [Clozapine and olanzapine have been reported to cause hyperglycaemia³⁷⁰⁵, diabetes mellitus and diabetic ketoacidosis more often than do other atypicals.³⁷⁰⁶ (Henderson & Ettinger, 2003, p. 107; Henderson ea, 2005)] gynaecomastia, galactorrhoea³⁷⁰⁷, amenorrhoea (high prolactin levels can lower oestrogen levels), and, in the longterm, possible osteoporosis³⁷⁰⁸. According to Goff and Shader (2003, p. 575) inadequate exercise, poor nutrition, cigarette smoking and polydipsia are risk factors for osteopenia in schizophrenic patients. Hummer ea (2005) used dual x-ray absorptiometry to determine bone mineral density and that male schizophrenics, but not females with that diagnosis, had low mineral density in the lumbar region. Minelli ea (2004) suggested that HRT can be used for significant menopausal symptoms. The use of HRT as a first-line prophylactic against osteoporosis in postmenopausal with has come under attack because of associated disorders, such as a slight increase in breast cancer.(Singh, 2003; Irish Medicines Board, 2003) There may also be an increased risk of stroke, particularly ischaemic stroke.(Bath & Gray, 2005) A large, population-based Canadian study (Gill ea, 2007) found that antipsychotic drugs may increase mortality in the elderly demented, typical (conventional) agents carrying a higher risk than atypical drugs³⁷⁰⁹, and the the risk developed within one month and lasted for up to 6 months³⁷¹⁰. Regular review of antipsychotic prescriptions are necessary in nursing homes and elsewhere.(Allred ea, 2007; Anonymous, 2007; Mashta, 2009) The risk for hyperlipidaemia is increased with atypical drugs, e.g. clozapine, quetiapine, risperidone, and olanzapine and with typical drugs (Koro ea, 2002; Meyer, 2003, p. 73; Olfson ea, 2006) Butyrophenones and aripirazole may be lipid neutral.(Meyer, 2003, p. 68; Olfson ea, 2006)

Dysphoria – can cause this in normals and patients; possibly improved by anticholinergic drugs

Sedation - tolerance to this effect occurs quickly (may give most of the dose at night); neuroleptics enhance respiratory depression from opiates and enhance the analgesic effects of morphine

Temperature - excesses of ambient temperature may lead to cold injury or to severe hyperpyrexia due to hypothalamic dysregulation

Foetus/Neonate - no firm evidence of problems

Eyes - opacities of lens and cornea, retinitis pigmentosa (especially thioridazine; the upper dose of thioridazine should not exceed 800 mg/day³⁷¹¹)

³⁷⁰³ Even community-based people on antipsychotics have an increased prevalence of metabolic syndrome and heightened risk for cardiovascular risk (Mackin ea, 2007) although choice of controls and direction of causality inferences remain problematic.

³⁷⁰⁴ ? Multifactorial aetiology: schizophrenia itself, centripetal obesity from medicines, interaction of H1 and 5HT_{2C} receptor blockade, and insulin resistance secondary to treatment. Adding an H₂ blocking agent or sibutramine (Henderson ea, 2005) has been suggested to reduce weight gain in patients on olanzapine. Poyurovsky ea(2003) report that reboxetine may attenuate weight gain in olanzapine-treated schizophrenics. Metformin (inhibits hepatic glucose production) is reported to abrogate weight gain, decreased insulin sensitivity, and abnormal glucose metabolism due to atypical antipsychotics.(Klein ea, 2006; Wu ea, 2008)

³⁷⁰⁵ CPZ causes hyperglycaemia more often than hypoglycaemia.

³⁷⁰⁶ All patients with schizophrenia should be routinely screened for diabetes no matter what medication (or none) they are receiving. Atypical-treated patients may be tested more often for diabetes than those treated with typical drugs.(Taylor ea, 2004) A systematic review and meta-analysis (Smith ea, 2008) found 'tentative' evidence that there is a 'small' increase in risk of diabetes when using second-generation antipsychotics for schizophrenia instead of older drugs, but methodological problems muddy the waters.

³⁷⁰⁷ Most antipsychotic drugs increase prolactin secretion.

³⁷⁰⁸ Associated with high prolactin levels.(O'Keane, 2001; Wieck & Haddad, 2003) Rey-Sánchez ea (2008) found that women with schizophrenia who were receiving antipsychotic drugs had reduced phalangeal bone mass that was associated with reduced levels of 25-hydroxyvitamin D and higher levels of parathormone and increased bone turnover.

³⁷⁰⁹ Kales ea (2007) found risks similar for atypical and typical drugs.

³⁷¹⁰ The editors pointed out that 'sensitivity analyses showed that unmeasured confounders may diminish or erase observed associations'. Without dismissing concerns about pharmacological over-control in nursing homes, such research does not control for the underlying cause of behavioural problems in demented patients.

³⁷¹¹ Beta-blocking drugs could push thioridazine levels up to levels dangerous to the eye.

Confusional States - especially in elderly and if combined with antiparkinsonian drugs

Reduced seizure threshold

Antiadrenergic - inhibition of ejaculation, postural hypotension; patients with postural hypotension should rise slowly, raising the end of the bed may help, and extreme cases may require an IV noradrenaline or metaraminol (**not** adrenaline) infusion³⁷¹²; CPZ combined with the ACE inhibitor captopril can lead to severe hypotension; also, hypotension can follow the combination of a low potency antipsychotic with certain anaesthetic agents, such as halothane, enflurane, and isoflurane; neuroleptics reverse the hypotensive action of guanethidine-like drugs by inhibiting monoamine reuptake

Anticholinergic - especially early on in treatment - dry mouth, blurred vision, mydriasis, constipation, urinary retention, impotence³⁷¹³, tachycardia, confusional states (via central effect), paralytic ileus (once common with use of prolonged deep narcosis)

Abstinence Syndrome - if these drugs are stopped suddenly there may experience nausea, vomiting, insomnia or headaches

Water intoxication – discussed elsewhere

Neuroleptic Malignant Syndrome³⁷¹⁴ (NMS) - high body temperature, generalised muscular rigidity³⁷¹⁵ (lead-pipe, even cog-wheeling), confusion, autonomic symptoms such as excessive sweating and salivation, tachycardia, changing blood pressure levels, tachypnoea, dyspnoea, unstable blood pressure, and incontinence. NMS is a relatively rare³⁷¹⁶, potentially lethal idiosyncratic reaction to therapeutic doses of antipsychotic drugs (typical > atypical), or tetrabenazine. (O'Shea, 1997) The mechanism may relate to antidopaminergic activity in the hypothalamus³⁷¹⁷ and/or basal ganglia, although the balance between serotonin and DA may be important, e.g. clomipramine is only a weak DA receptor antagonist but has been associated with NMS. (Haddow ea, 2004) Many features of the serotonin syndrome are shared with NMS. (Ames & Wirshing, 1993) NMS has been reported to follow stopping levodopa or dopaminergic drugs³⁷¹⁸. (Meltzer & Fatemi, 1998) Most reports of NMS occurring in patients on combined lithium and antipsychotic medication have been associated with dehydration and high serum lithium levels. (APA, 2002, p. 391) The symptoms can arise any time after starting treatment, but usually earlier rather than later. They develop over 1-3 days and tend to subside in about a week, or up to 3 weeks with depot preparations. Re-exposure does not inevitably result in another attack. Triggering of an attack may require the presence of fatigue, dehydration, infection, hyponatraemia, catatonia (it has been suggested that lethal catatonia in unmedicated patients is the same as NMS), or organic brain disease, but this is controversial. Rapid dose escalation may be a factor. Pneumonia may occur³⁷¹⁹. NMS has occurred in cases with Parkinson's disease, when DA agonists were abruptly withdrawn, and in a patient who received metoclopramide³⁷²⁰. DA deficiency in both the basal ganglia and the hypothalamus may underlie NMS. Laboratory investigations merely show non-specific secondary changes, e.g. a neutrophil leucocytosis in the absence of

³⁷¹² Giving adrenaline will lower the blood pressure further because of beta-adrenergic stimulation leading to vasodilatation – the alpha-1-adrenergic properties are blocked so one does not get the usual pressor effect; a similar effect may occur if a low potency antipsychotic is given in the presence of phaeochromocytoma. Asthmatic receiving antipsychotics may require episodic beta-adrenergic medication and should be aware of the potential dangers of receiving adrenaline during acute attacks.

³⁷¹³ Asking about sexual problems before prescribing antipsychotic medication may improve detection of secondary sexual dysfunction following prescription by reducing embarrassment – it may also improve compliance. (Smith ea, 2002)

³⁷¹⁴ Described in 1960 by J Delay, P Pichot and T Lempérière.

³⁷¹⁵ Rigidity may be absent in patients taking atypical drugs.

³⁷¹⁶ Incidence in different reports varies from 0.2-1.0% and the mortality is put at about 20%.

³⁷¹⁷ Injecting antipsychotic drugs into the hypothalamus has produced hyperthermia.

³⁷¹⁸ Never stop high doses of anti-parkinsonian drugs abruptly!

³⁷¹⁹ Somatic illness may predispose to NMS and many such disorders may **mimic NMS**, e.g. malignant hyperthermia (post-anaesthesia), lethal catatonia, serotonin syndrome, tetanus, epileptic status, porphyria, subcortical cerebral lesions, CNS infection, and heat stroke (dry skin, flaccid muscles, low blood pressure). The main differential diagnoses to consider in cases of tetanus are tetany, strychnine poisoning, phenothiazine toxicity, and meningitis.

³⁷²⁰ A DA receptor antagonist, acting on nigrostriatal pathway but not mesolimbic system, and having minimal antipsychotic effect.

infection, elevated liver transaminases, elevated creatinine phosphokinase³⁷²¹ and serum potassium (due to necrosis of voluntary muscle), reduced serum iron, and the EEG may show non-specific slowing. Postmortem studies give normal results.

Risk factors for NMS (after Ahuja & Cole, 2009)

Past personal or family history of NMS

Lewy body dementia, disorder of basal ganglia, catatonia, drug abuse

Dopamine antagonists – anti-emetic, sedative, antipsychotic*

Young, male, activity/tiredness, dehydration/electrolyte imbalance/humid, warm atmosphere

Low serum iron, raised creatinine in psychosis

*Starting with too high a dose or too fast, IM/IV, depot, suddenly stopping antipsychotic drug

The differential diagnosis includes rhabdomyolysis from other causes, severe dystonic reactions, malignant hyperthermia (CO₂ levels are typically raised in this disorder and are normal in NMS), catatonia, CNS infections³⁷²² or lesions, heat stroke, allergic drug reactions, toxic encephalopathy, hyperthyroidism, pheochromocytoma, serotonin (5-HT) syndrome, tetany and Parkinson's disease. Complications include metabolic acidosis, dehydration, shock, coagulopathy, acute myoglobinuria and renal failure, respiratory failure and pneumonia, and cerebellar damage. Management includes stopping the offending drug, cooling the body, treating any infection or organ failure, replacing body fluids, and, if prompt improvement doesn't occur, considering ECT. (Troller & Sachdev, 1999; Ozer ea, 2005) The following drugs may be used on their own or together, although there is a report that contrasts to most others suggesting that they can prolong the disorder (Rosebush ea, 1991): Bromocriptine (Parlodel), 60 mgs per day - acts centrally as a DA agonist. Dantrolene (Dantrium, 10 mgs/Kg/day) acts peripherally to reduce skeletal muscle tone. It may cause liver toxicity (Marangell ea, 2003, p. 1092) and should be avoided in patients with poor hepatic function. Kellam (1987) suggested the following treatment for NMS: try dantrolene with either amantadine or bromocriptine or both - if no response, give IV lorazepam (especially if catatonic symptoms are marked) - if DA agonists have cured the rigidity and pyrexia but psychotic symptoms persist, one might consider ECT.³⁷²³ Some authors caution delaying ECT until the syndrome has subsided. Other suggested drug therapies have included L-DOPA and amantadine.³⁷²⁴ There may be a relationship between NMS and malignant hyperthermia, although this is strongly disputed. (Sackeim, 2003, p. 535) The latter trait is inherited as an autosomal dominant³⁷²⁵ and is an abnormal muscle reaction to anaesthetics. Also, White (1992) points out that the occurrence of NMS and catatonia as separate episodes in the same patient suggests that they may be different aspects of the same diathesis. A clustering of cases in South Wales during the early 1990s added to the aetiological debate. (Huckle ea, 1993) Temperature and blood pressure should be routinely monitored in disturbed patients requiring rapid sedation and the co-prescription of short-acting BZDs alongside antipsychotic drugs may help to avoid cumulative dosing.

³⁷²¹ This has poor diagnostic reliability because it is also raised after IM injection, injury, use of restraints, oral neuroleptics, acute dystonia, acute psychosis, acute myocardial infarction, various muscle diseases, rhabdomyolysis secondary to drug abuse, etc. Urinary myoglobin is increased in NMS, PCP/cocaine/LSD users, and with restraints.

³⁷²² An NMS-like state can be caused by meningoencephalitis of almost any aetiology, 'so that the presence of a neuroleptic is merely coincidental'. (Friedman & Fernandez, 2004, p. 174)

³⁷²³ Consider using non-depolarising muscle relaxant, e.g. atracurium or mivacurium. The effect of ECT varies from effective to ineffective to precipitation of cardiac arrhythmias. In 55 published cases of NMS who were given ECT (Troller & Sachdev, 1999) 40 responded of which 25 achieved remission and 11 had a partial response.

³⁷²⁴ As stated above, a similar syndrome to NMS follows withdrawal of DA agonists, such as L-DOPA, amantadine or bromocriptine, in patients with Parkinson's disease.

³⁷²⁵ Diagnosed by caffeine- or halothane-induced muscle contractures on muscle biopsy; incidence of 1 in 12,000 children and 1 in 40,000 adults; gene localised to 19q12-13.2; similar condition found in swine.

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The 'hyperthermic malignant syndrome', which resembles NMS, may follow surgery in patients with Parkinson's disease who have had to stop L-DOPA³⁷²⁶. This can be treated with IV or SC apomorphine (DA agonist). In fact, Colosimo ea (1994) suggest using apomorphine to replace L-DOPA in Parkinson's disease patients undergoing GIT surgery.

CNS

Antipsychotic drugs, from the point of view of this discussion, may be seen as acting at three important sites within the central nervous system (CNS): DA receptors in limbic system - hence antipsychotic effect; hypothalamico-pituitary - hence raised prolactin; and extrapyramidal system - the main clinical effects are:

Bradyphrenia – sluggish thinking – may respond to anticholinergic drugs.

Akinesia is a very common and usually extremely early adverse effect of antipsychotic medication. There is less than normal spontaneity of movement or facial expression, there is *no hypertonia*, and the patient feels tired, indifferent, sad, or 'like a zombie'. It must be differentiated from the apathy of depression or schizophrenia. Treatment involves dose reduction or use of anticholinergic drugs.

Acute dystonia³⁷²⁷ – Aetiological theories involve presynaptic DA autoreceptor blockade or increased striatal anticholinergic activity. Sustained contraction of muscles of neck, mouth, tongue, or occasionally other muscle groups that is subjectively distressing and often painful.³⁷²⁸ Examples are oculogyric crisis³⁷²⁹, blepharospasm, glossopharyngeal dystonia³⁷³⁰, tortipelvis, lordosis, scoliosis, opisthotonus, and twisting of mouth or rotation of neck.³⁷³¹ Bizarre movements are sometimes mistaken for 'hysteria' or malingering. Acute first-episode psychotic patients are more likely to develop acute dystonia if they are relatively young and have negative symptoms. The young³⁷³² male (well muscled) is the classic victim but the association with male sex is questionable. Other drugs that have been reported to cause acute dystonia include metoclopramide, prochlorperazine, SSRIs, cocaine,(Catalano ea, 1997) antihistamines in OTC cold and cough cures in children(Owens, 2000), and, arguably, tetrabenazine, mefanamic acid, oxtomide, flunarizine, and cinnarizine³⁷³³. Flecainide, a substituted benzamide and class Ic antiarrhythmic, has been reported to 'possibly' cause oro-facial dyskinesia in one case.(Miller & Jankovic, 1992) Even though most cases subside spontaneously within hours, early intervention is required for these intense experiences. Treatment is with parenteral anticholinergic (e.g. procyclidine [Kemadrin] 5-10 mg IV) followed by oral agent such as biperiden (Akineton). Benzodiazepines (e.g. lorazepam 1 mg IM or IV) are second-line interventions. Reducing the dose of antipsychotic drug may lead to a transient worsening of dystonic movement, but about 50% of the movements will improve or disappear eventually.(Barrett, 1993)

Tardive dystonia might possibly be due to a neuroleptic-induced frontal lobe syndrome. It may be impossible to differentiate from TD but anticholinergic drugs may help some cases with tardive dystonia. Median of 5 years exposure to antipsychotic drugs but can occur as early as 3 weeks. Face and neck are main areas affected.(APA Task Force on Tardive Dyskinesia, 1992) Similar movements to primary torsion dystonia. Blepharospasm may be the presenting sign. Anticholinergic drugs, tetrabenazine, reserpine, clozapine, or stopping the offending drug are all possible management strategies. Most cases are males who have a relatively short exposure to antipsychotics. Partial response to therapy is often the situation. Clozapine has been suggested for

³⁷²⁶ L-DOPA is poorly water soluble, so can't be given parentally.

³⁷²⁷ Described in 1695 as post-encephalitic ocular spasm by J P Albrecht.

³⁷²⁸ The reaction occurs early, is more marked with haloperidol than with CPZ and is very rare with clozapine.(Owens, 2000)

³⁷²⁹ This can occur late in treatment. Psychosis may worsen during a crisis.(e.g. Thornton & McKenna, 1994)

³⁷³⁰ Dysarthria, dysphagia, breathing problems, cyanosis.

³⁷³¹ Children can develop opisthotonos, scoliosis, lordosis, or writhing movements.

³⁷³² The incidence of dystonia declines by 4%/year and is very rare after 40 years of age.(Arana ea, 1988)

³⁷³³ The latter two drugs, vestibular sedatives, are piperazine derivatives.

refractory, persistent, life-threatening cases (e.g. laryngeal dystonia). Cunningham Owens (2004, p. 269) believes that it “should always be considered”. Botulinum toxin can be used for circumscribed tardive dystonic syndromes, such as laryngeal dystonia, but injections need to be repeated every 3-6 months. Thalamotomy, pallidotomy, and deep brain stimulation of the globus pallidus are surgical approaches to managing refractory cases.

Dystonic storm³⁷³⁴ is a severe exacerbation of dystonic spasm that can lead to myoglobinuria and renal failure. It usually persists for days, requires management in an ICU, and may occur for no obvious reason or is precipitated by intercurrent illness, including infection.

Tardive dysmetria is a controversial term (Sachdev, 2004, p. 152) for chronic disturbance of attention, concentration and executive cognitive activity that accompanies tardive movement disorder.

Dopamine supersensitivity psychosis (tardive psychosis), (DSP) variously defined as the emergence of agitation, confusion, and affective instability after longterm neuroleptic therapy is stopped (Chouinard & Sultan, 1990) or whilst on chronic neuroleptic treatment. (Kay & Tasman, 2006, p. 393) Typical schizophrenic thought disorder is said to be absent. Suggested treatment for DSP is with anticonvulsant drugs. The existence of DSP is controversial. Distinguishing between an exacerbation of the underlying psychosis and DSP would be difficult, although a patient given longterm neuroleptic drugs for, say, Tourette disorder, might pose less of a diagnostic problem.

Tardive dysbehaviour disorder, the occurrence of increased activity, aggression, screaming, insomnia and so on after stopping long-term antipsychotic drug treatment, (Gualtieri et al, 1984) is another controversial disorder.

Acute akathisia³⁷³⁵: The mechanism may be one of DA receptor blockade in the frontal cortex innervated by the mesocortical DA pathway, although pathogenesis is uncertain.

Akathisia

May be responsible for non-compliance with medication, violence or even suicide

Occurs in both medicated and unmedicated Parkinsonism

Occurs in about 20% (12.5-45%) of patients on antipsychotic drugs

Clozapine less likely to cause akathisia

Other drugs reported to cause acute akathisia: lithium, calcium antagonists, carbamazepine, ethosuximide, methysergide, reserpine, tetrabenazine, SSRI antidepressants, TCAs, amoxapine, and buspirone

Other serotonin reuptake inhibitors (SRIs) such as ritanserin and cyproheptadine may have similar potential

Minimal evidence that low dose mianserin (a 5-HT₂ antagonist) may alleviate akathisia, but it has also been blamed for akathisia!

Low serum iron might be a risk factor?

The affected person complains of restlessness or inner tension. There may be subjective and objective components, but the absence of the subjective element (pseudoakathisia) does not negate the diagnosis, (Sachdev, 2004, p. 152) although objective-only cases are more likely in chronic and tardive forms of akathisia. Severe cases are unable to sit still for even a brief moment. Lying down offers some relief, unlike what happens in restless legs syndrome. However, the supine case may still show legs crossing and uncrossing, shifting of the position of the trunk, and various other movements. Anticholinergic drugs or BZDs may give some benefit but fat-soluble beta-blocking drugs like propranolol (Inderal) are suggested as the ideal treatment. Newer treatment options include low-dose

³⁷³⁴ *Status dystonicus*.

³⁷³⁵ Motor restlessness (Gk, ‘not to sit’) - the term was coined by the Czech neuropsychiatrist Ladislav Haskovec (1866-1944) in 1901. Akathisia was first reported as a complication of antipsychotic medication by Hans Steck (1954) a psychiatrist at Céry-Lausanne.

mirtazapine (15 mg once daily), mianserin, and cyproheptadine.(Poyurovsky, 2010)
Clonidine and amantadine might be tried if other options fail.

Withdrawal akathisia develops days to weeks after stopping or reducing the dose of an antipsychotic drug. However, akathisia following removal of a drug that suppresses akathisia does not fit this definition.

Tardive³⁷³⁶ akathisia does not always respond to anticholinergic drugs or to reducing the dose of antipsychotic drugs. Usually of 'pseudoakathisia' form, i.e. there is no subjective component of restlessness. These terms are often used in different (and confusing) ways, e.g. tardive is sometimes used synonymously with withdrawal akathisia, i.e. appearing when longterm antipsychotic drug therapy is stopped; it is also used to mean persistence of the symptoms despite stopping the offending medication. Also, pain or burning in the oral or genital regions has been included in this category.(Ford et al, 1994) Like the acute syndrome, tardive akathisia is usually relieved by lying down. Tetrabenazine or reserpine may improve some cases of tardive akathisia.

Pseudoakathisia is an unfortunate term that may mean tardive dyskinesia of the lower limbs or that there is no subjective sensation of restlessness.

Hemiakathisia (affects one half of body) and **monoakathisia** (one limb involved) are curiosities. Although reported in relation to drug therapy, they should lead one to consider a physical cause.

Secondary akathisia may be due to Parkinson's disease, cerebral trauma, damage to the lenticular nucleus or subthalamic nucleus, or encephalitis lethargica.(Sachdev, 2004, p. 133)

(‘Pseudo’) Parkinsonism consists of mask-like facies, dribbling, bradykinesia, lack of associated movements like arm swinging whilst walking, rigidity, pill-rolling tremor, cogwheel rigidity³⁷³⁷. Whilst forward flexion of the spine is typical, some cases may stand stiff and upright³⁷³⁸ whilst others may even bend backwards. Extrapyramidal rigidity can be lead-pipe (persistent resistance to passive movement) or cogwheel (succession of resistances). Treat with anticholinergic drugs or lower dose of offending drug. Tolerance often develops to drug-induced Parkinsonism. Older women are the classic victims. Wilson and Primrose (1986) suggested that drug-induced Parkinsonism might increase the chances of later developing Parkinson's disease. There is some evidence for this.(Chaudhuri & Nott, 2004) In a graph with arms showing clinical response against dose of antipsychotic drug there is a point where DA and Ach are widely separated, the point of maximum Parkinsonism. Above and below that point these two activities come closer together so that Parkinsonism becomes less at lower and higher doses. This accounts for the well-known clinical phenomenon of an increase in Parkinsonism as the dose of neuroleptic is reduced! EPS are made worse by anxiety and lessened by sleep.

Numerous drugs have been reported as causing Parkinsonism, e.g. antipsychotic drugs, vestibular sedatives (cinnarizine and flunarizine), and reserpine, disulfiram, manganese, and valproate (after at least 12 months treatment). Whilst most cases are reversible, some may represent unmasking of idiopathic Parkinson's disease.(Chaudhuri & Nott, 2004) Amiodarone may cause tremor.(Hotton & Clough, 2004)

Tardive dyskinesia³⁷³⁹ (TD) is a term that may encompass all persistent abnormal involuntary movements presumed to may be due to chronic neuroleptic use, or it may apply to the classic form of TD, so-called tardive stereotypy. It is hypothesised to be due to supersensitive DA receptors but there is much we do not understand about its

³⁷³⁶ Late-onset.

³⁷³⁷ Get patients to hold pen and stare at it as he squeezes it, now test other arm by moving joints passively as his concentration is diverted elsewhere.

³⁷³⁸ Poker spine.

³⁷³⁹ Fr *tardif*, late. The first modern description may have been that of Matthias Schönecker in 1957 (of Essen-Brobeck) and the term 'tardive dyskinesia' was proposed by Arild Faurbye (1907-1983) of St Hans Psychiatric Hospital Roskilde (Denmark) and co-workers in 1964.(see Mattay & Casey, 2003, p. 558) *The movements of TD decrease during voluntary action and therefore patients can usually manage to feed themselves.*

pathogenesis.(Manschreck ea, 2003, p. 207) Whilst GABA underactivity has been suggested as being a factor in the genesis of TD, treatment aimed at correcting this³⁷⁴⁰ has produced inconsistent results. It can develop months (Dulcan, 1996) to years after starting neuroleptics (or amoxapine, prochlorperazine, metoclopramide, or SSRIs).(O'Shea, 1997; Gerber & Lynd, 1998) Sandler (1996) reported TD in association with fluoxetine treatment. Mattay and Casey (2003, p. 560) hold that while lithium and TCAs may worsen TD they probably do not cause it. Indeed, there is some suggestion that lithium therapy may reduce the likelihood of TD when give to patients with affective disorders.(Mattay & Casey, 2003, p. 564) TD may not a single entity and about 90% are mild.(APA, 2002, p. 374) Store-depleting antipsychotic drugs like reserpine and tetrabenazine, while causing other EPS, do not cause TD. Patients with affective disorders who are given neuroleptics (disputably, depressed patients may be at greater risk than schizophrenic patients – Yassa ea, 1992; Larkin & Gervin, 1998 – but not all studies agree: Twamley ea, 2003, p. 790) and patients with non-psychotic disorders given antipsychotic drugs can develop TD. In patients of 55 years or older with bipolar affective disorder, the ones with involuntary movements were not distinguished from those without them by past or current exposure to antipsychotic drugs, anticholinergics, or carbamazepine, but they had poorer cognitive function, had fewer major depressive episodes, and had received briefer exposure to lithium.(Waddington and Youssef, 1988) The association between involuntary movements and cognitive dysfunction parallel that found in schizophrenia by the same authors. However, there is a complex inter-association between TD, cognitive impairment, certain negative symptoms and formal thought disorder.(Davis ea, 1992) The most common form is the facio-bucco-labio-lingual- masticatory syndrome. TD is characterised by writhing movements. It is more common with age³⁷⁴¹, anticholinergic drug given in addition³⁷⁴², possibly female sex, depot neuroleptics³⁷⁴³, and perhaps early Parkinsonism. Risk factors found at Yale (Anonymous, 1993) for TD were increased age, being black, being on higher doses of antipsychotic drugs³⁷⁴⁴, and being right-handed or ambidextrous. The first 5 years of treatment with neuroleptics was the period of greatest risk for TD³⁷⁴⁵, but the risk continued to increase with continued exposure.

Problems with much of the TD research are that more antipsychotic drug for longer periods may have been a result of greater illness severity which might itself have been associated with greater risk for TD and the lack of suitable matched unmedicated controls.

Whilst studies have suggested that vulnerability to TD may vary by race (e.g. African Americans), confounding may have occurred due to assignment of ethnicity in a multiracial society, and other factors such as medication choice and dosage, tobacco, alcohol³⁷⁴⁶, diet, and genes must all be taken into account.(Swartz ea, 1997) There have been reports of increased levels of IGA and IGM in schizophrenics with TD and more common and longer drug-free periods in the more severe forms of TD. Suddenly stopping the offending drug may even make matters worse³⁷⁴⁷. TD is made worse by anxiety.

³⁷⁴⁰ Valproate, BZDs, baclofen, and progabide.

³⁷⁴¹ Fenton(2000) suggests that 40% of schizophrenic patients aged at least 60 years have spontaneous dyskinesia.

³⁷⁴² Controversial - TD may improve if they are withdrawn.

³⁷⁴³ Possibly this may be because of greater compliance or more severe illness. However, a meta-analysis has shown no excess of NMS, TD or EPS with depot over oral neuroleptics.(Guinta, 1997)

³⁷⁴⁴ Does this reflect illness severity?

³⁷⁴⁵ 32% of patients affected by then.

³⁷⁴⁶ Cocaine or a long history of alcohol abuse may itself increase risk for TD.(De Leon & Jankovic, 2004)

³⁷⁴⁷ Stopping an antipsychotic may lead to gradual decline in TD, although TD may worsen initially (*withdrawal-emergent dyskinesia*, to distinguish it from treatment-emergent dyskinesia). *Withdrawal-emergent* dyskinesia may either resolve over some weeks or may not resolve, the latter presumably representing cases that were latent or simply suppressed by D2 blockade. Withdrawal-emergent dyskinesia may follow a change from a typical to an atypical antipsychotic.

Motor disorders may have more to do with mental illness that is modified by drugs (*perhaps brought forward in time*) than any direct effect of the drugs. (Owens ea, 1982; McCreadie ea, 1996; Fenton, 2000; Halliday ea, 2002) Modestin ea (2008) followed up inpatients on typical antipsychotics and/or Clozapine from 1995 to 2003/4. Their findings are shown in the box.

Evolution of neuroleptics-induced extrapyramidal syndrome in inpatients on long-term antipsychotic drugs (Modestin ea, 2008)

N assessed 1995 = 200

N assessed 2003/4 = 83 (63 had died)

% with akathisia in 1995 and 2003/4 = 14 and 14 respectively

% with TD in 1995 and 2003/4 = 24 and 13 respectively

Only association with evolution of TD = illness duration

No significant association between changes in TD ratings and and long-term treatment with typical, clozapine or other atypical antipsychotic drugs

Considerable fluctuations intra-individually in extrapyramidal signs even while overall prevalence remained the same

Current atypical and clozapine associated with increase in and reduction in akathisia respectively

Tendency for increased Parkinsonism to be associated with current treatment with typical drugs

Research on Indian schizophrenic patients suggests that TD is due to schizophrenia *per se*. (McCreadie ea, 1996) Certainly, TD was described long before modern drugs became available (Kraepelin, 1919; Farran-Ridge, 1926) and it occurs even today in unmedicated psychosis. Adolescents with schizotypal disorder were found to have an excess of movement disorder that progressed with time and that correlated with prodromal psychotic symptoms. (Mittal ea, 2008) Pappa and Dazzan (2009) performed a systematic review of spontaneous abnormal movements in antipsychotic-naïve first-episode psychosis subjects (13 relevant studies found) and found spontaneous dyskinesia and parkinsonism median rates of 9% and 17% respectively; presence of spontaneous abnormal movements may be associated with negative symptoms and cognitive dysfunction; and the authors suggest that spontaneous abnormal movements are intrinsic to schizophrenia. McCreadie ea, (2002) using MRI, looked at chronic unmedicated Indian schizophrenic patients and normal controls. The left lentiform nucleus was 11% larger in dyskinetic patients v controls, and the right lateral ventricle-hemisphere ratio was 33% larger in patients without dyskinesia v controls. As controls age the volume of caudate and lentiform nuclei shrink, a pattern not seen in the patients. The authors suggested that dyskinetic patients have striatal pathology, whereas cortical atrophy is more pronounced in non-dyskinetic cases. A generally accepted figure is that new cases of TD occur at a rate of 2.5% of patients/year on longterm treatment, and 10% of elderly patients develop TD within one year. The limbs, especially the extremities, may be the sites of rudimentary isolated choreiform movements. Early signs of TD include lingual myokymia³⁷⁴⁸ (worm-like tongue movements), tic-like movements of the lips and face, and rapid blinking. The 'bon-bon' sign is when the tongue goes beyond the teeth it makes movements akin to sucking a sweet (bulging of cheek). 'Fly-catcher' sign involves jerky protrusions of the tongue at the corners of the mouth. Severe cases are unable to hold their tongue out for 30 seconds. 'Bridling movements' are irregular retractions of the angles of the mouth. The eyebrows may be raised.

Other manifestations (e.g. Marsalek, 2000)

³⁷⁴⁸ **Myokymia** or 'live flesh' is also the name for a familial innocuous orbicularis oculi (or other muscle) twitch. The term is also used to refer to rare sinuous, wavy or fine lower facial movements due to lesions of the brainstem.

Chewing and grinding of jaws
 Blepharospasm
 Blepharoclonus
 Grimacing (reminiscent of Huntington's disease)
 'Piano-playing' movements of fingers (as in Sydenham's chorea)
 Hand clenching
 Dorsiflexion of great toe
 Shoulder hugging
 Hip flexion
 'Copulatory' movements (pelvic thrusting)
 'Axial hyperkinesia' (involvement of postural muscles)
 Involvement of the respiratory or deglutition muscles (may emit bizarre animal grunts)
 Aerophagy with belching
 Mouth ulcers
 Tardive oculogyrus (conjugate ocular deviation)
 Weight changes

The patient is usually less disturbed than the onlooker. Complications of TD, some of which are very rare, include dental problems, ulceration of lips/tongue, dysphagia, tempormandibular joint degeneration, aspiration pneumonia, dysphonia, hypertrophic lingual and truncal musculature, raised creatine kinase levels³⁷⁴⁹, myoglobinuria. Dean and Thuras (2009) examined the death certificates of American patients who had been repeatedly assessed for TD during life. TD was significantly associated with an increase in mortality, more so if they had been taking conventional (versus atypical) antipsychotics and particularly if they were older.

Differential diagnosis of neuroleptic-induced TD

Other drug effects³⁷⁵⁰
 Schizophrenic mannerisms and stereotypies
 Dental problems³⁷⁵¹
 Senile dyskinesias such as Meige's
 Anoxia
 Hepatic failure
 Renal failure
 Huntington's disease
 Wilson's disease
 Hyperthyroidism
 Hypoparathyroidism
 Post-encephalitic states
 Chorea gravidarum
 Sydenham's chorea
 SLE
 Torsion dystonia
 Tumours

Schizophrenia, especially if accompanied by a 'defect state' with cognitive deficit and negative symptoms, may militate against awareness of TD. Patients with TD may show an excessive release of developmental (primitive/neonatal) reflexes, e.g. grasp, snout,

³⁷⁴⁹ A raised **creatinine kinase** level may be due to NMS, hyperthermia (e.g. malignant catatonia or serotonin syndrome), muscular dystrophies, rhabdomyolysis (restraints, rigidity/dystonia, ischaemia, agitation, isotonic exercise, psychosis, IM injections), damaged myocardium (MB fraction). (Ahuja & Cole, 2009)

³⁷⁵⁰ Antihistamines, antimalarials, phenytoin, heavy metals, L-DOPA, and sympathomimetics.

³⁷⁵¹ E.g. ill-fitting dentures/edentulousness.

corneo-mandibular, and glabellar reflexes, suggesting perhaps anomalies in brain development rather than cerebral deterioration from a once normal level of functioning. One may stop the antiparkinsonian medication³⁷⁵², reduce the dose of the antipsychotic drug or stop it altogether, or try sulpiride, tetrabenazine³⁷⁵³ or an atypical agent like clozapine (with or without clonazepam). TD has returned following cessation of clozapine. Ondansetron, a 5-HT₃ receptor antagonist, has been reported in an open-label study to improve AIMS scores in patients with TD.(Sirota ea, 2000) Other drugs that have been said to cause TD-like movement disorders are L-dopa (a hyperkinetic syndrome³⁷⁵⁴), amphetamine (dyskinesia), phenytoin, antihistamines, TCAs, and the contraceptive pill. Certain ‘typical’ antipsychotics cause less movement disorder, e.g. thioridazine and sulpiride,(Livingston, 1994) although cases of TD have been described in patients on sulpiride.(Cullen & Daly, 1996) Interestingly, Shiloh ea (1997) and Agelink ea(2004) advocate adding sulpiride (circa 600 mg/day) to clozapine in partially responsive schizophrenia³⁷⁵⁵. Waddington and Youssef (1985) found TD in 41% of chronic schizophrenics. The prevalence increased with age and was independent of the length of time on antipsychotic drugs and of the average daily dose over this period. They found no significant difference in prevalence between the sexes. Waddington ea (1985) reported that schizophrenics with TD were more intellectually impaired, had more negative symptoms, and were older than those without TD. Prolonged neuroleptic treatment of young rats is associated with late-onset orofacial movement; however, such movements occur spontaneously in untreated old rats. Structural brain changes consequent to ageing and disease processes may be associated with the emergence of orofacial dyskinesia, even in the absence of exposure to antipsychotic drugs. Vitamin E (a membrane-soluble antioxidant) enjoyed a brief period of promise as an anti-TD agent because of the theory that antipsychotic drugs increase catecholamine metabolism (increasing free radical production) and enhance trace metals, both mechanisms producing TD via cytotoxicity.(Adler ea, 1999) There are claims that melatonin may improve AIMS scores, possibly by an antioxidant effect and attenuation of both striatal DA activity and release of DA from the hypothalamus.(Shamir ea, 2001) Controversially, many practitioners simply increase the dose of neuroleptic in order to mask TD. This practice may be necessary in life-threatening cases. Phenylketonurics may *possibly* be at increased risk for TD.(Mattay & Casey, 2003, p. 563) It is suggested that TD may be associated with reduced clearance of ingested phenylalanine, a large neutral amino acid, and there is some evidence that giving branched chain amino acids (e.g. valine, leucine, isoleucine: Tarvil) reduces the symptoms of TD.(Richardson ea, 1999, 2003) It has been remarked that many drug treatments for TD do better in open trials than in methodologically rigorous research.(APA, 2002, p. 375) Deep brain stimulation and bilateral posteroventral pallidotomy have produced useful results in extreme cases of TD.(Mattay and Casey, 2003, p. 567) In conclusion, TD can be a side effect of medication or ‘a motor symptom of mental disorder in its own right’.(Sims ea, 2000) **Pisa syndrome**³⁷⁵⁶: tonic flexion of the trunk to one side, accompanied by its slight rotation, in the absence of other concomitant dystonic symptoms. The condition is exacerbated by walking. It is arguably a dystonia³⁷⁵⁷ or variant of TD. May improve when antipsychotic drugs are withdrawn but anticholinergic drugs are unhelpful. **Tardive Tourette’s disorder** (tardive tourettism) – has emerged during neuroleptic therapy. There are multiple tics and vocalisations, even echolalia and coprolalia, sometimes with TD-like movements. **Tardive myoclonus** – uncommonly myoclonus is the predominant feature of TD.

³⁷⁵² Improvement, if it occurs, may take months.

³⁷⁵³ 12.5 mg bid to start, titrating to max of 50 mg tid in weekly intervals.

³⁷⁵⁴ Adding a dopamine agonist to L-DOPA reduces the risk of dyskinesia but increases cost and potential side effects.(LeWitt, 2008)

³⁷⁵⁵ Other selective D₂ antagonists such as pimozide and amisulpride have also been suggested.(Travis, 2002)

³⁷⁵⁶ Described by Ekblom in 1972 (one of his 3 eponymous syndromes).

³⁷⁵⁷ Affects one side of trunk – if bilateral it would cause arching.

Tardive tremor – variant of TD with absence of other features of Parkinsonism; may respond to tetrabenazine.(Stacy & Jankovic, 1992)

Rabbit syndrome - this perioral tremor may not be part of TD. It may indeed represent a variant of drug-induced Parkinsonism.(Chaudhuri & Nott, 2004, p. 66) There is a fine, rapid movement of the lips (3-6 Hz) that mimics the chewing movements of a rabbit. It occurs late during antipsychotic drug therapy. Rabbit syndrome may occur in 4% of such patients who are not receiving concomitant anticholinergic drugs. An anticholinergic drug may be helpful. One case responded to olanzapine.(Durst ea, 2000)

Blepharospasm-romandibular dystonia syndrome³⁷⁵⁸ (BODS, Meige's) BODS must be distinguished from hysteria and TD. Different components of the syndrome can occur together or in isolation. It may be precipitated by antipsychotic drugs, including risperidone.

BODS

Usually occurs in mid-life

Women are affected more often than are men

Dystonic contractions of jaw and facial muscles (often including platysma)

Difficulties in mastication, speaking and swallowing

May bite tongue or mouth

Jaw may dislocate (sometimes)

Blepharospasm may cause functional blindness

Neuroleptic-induced catatonia might respond to amantadine 100 mg bid given for several weeks and stopping the offending drug may be followed by gradual recovery

Recent research on tardive dyskinesia (TD)

1982. Richardson and Craig point out that the observed coexistence of neuroleptic-induced Parkinsonism and TD argues against any generalised hyperdopaminergic state since the increase in dopamine should improve the Parkinsonism!

1983. Early acute drug-induced EPS increases risk for TD.

1984. Expect a 50% reduction in dyskinetic movement in most patients by 18 months after stopping antipsychotic drugs.

1985. Postmortem study showed no difference in D1 or D2 receptor binding in schizophrenics with and without movement disorders, a finding interpreted as being against DA supersensitivity in TD.

*Transient withdrawal dyskinesia and TD reported in 8 to 51% of antipsychotic drug-treated children and adolescents.*³⁷⁵⁹

1987. Unlike adults, dyskinesias have been reported within months of starting neuroleptics in younger patients.

1988. Increasing age is associated with increasing prevalence of dyskinesia.

1989. Risk of non-compliance after informing American patients of risk of TD may be exaggerated.

1991. 16 year follow up of females with 'non-organic brain syndromes' from a mental hospital: prevalence of TD rose from 18.4% to 46.5% - associated with neuroleptic dose and enlarged cerebral ventricles

Retrospectively, of those on neuroleptics 58% had chronic-persistent TD and the rest had intermittent pattern; chronic-persistent pattern associated with increased age and presence of non-orofacial dyskinesia at baseline

1992. APA Task Force estimate incidence of TD as 5% per year of exposure to neuroleptics among young adults and 30% after 12 months of exposure among elderly patients.

³⁷⁵⁸ Described by a French neurologist, Henri Meige; or Breughel's syndrome - the latter after the painter of 'infernal monsters', Breughel or Breughel the Elder, Dutch artist, d. 1569: actually described by Marsden in 1976. Moore(2001) states that Breughel's syndrome differs from Meige's syndrome by the absence of blepharospasm and the presence of oromandibular dystonic yawning-like movements. Authors differ!

³⁷⁵⁹ Stopping/reducing the dose of a conventional/typical antipsychotic or switching to an atypical antipsychotic (but stopping clozapine has led to withdrawal dyskinesia and dystonia: Ahmed ea, 1998) can sometimes cause a withdrawal dyskinesia (or unmask a dyskinesia suppressed by the typical agent) that usually resolves in about six weeks,(Munetz ea, 1989) although this author has treated a persistent case of respiratory dyskinesia in an elderly male by reintroduction of the typical antipsychotic followed by very slow withdrawal.(O'Shea, 2001) Withdrawal dyskinesia is typically seen in children. Treatment of withdrawal dyskinesia or dystonia may include re-starting the drug followed by a slow taper.

1993. In chronic schizophrenic patients, both oro-facial and trunk and limb dyskinesia are associated with negative symptoms, but only oro-facial dyskinesia showed a significant increase in prevalence with increasing age; patients with negative symptoms tend to develop oro-facial dyskinesia at an earlier age.

Diabetes mellitus may be a risk factor for TD.

1994. Young Nigerian schizophrenics who never had neuroleptics did not have TD and TD in younger schizophrenics was related to longer duration on these drugs.

10-year follow-up in Hungary: overall prevalence of TD (30%) varied little; some cases experienced remission whilst others developed TD during the study; outcome not significantly related to neuroleptic treatment or age; TD remains stable; and authors suggest maintaining neuroleptic treatment if it is keeping psychosis under control.

Rate of dyskinesia in mentally retarded women is negatively recorded with IQ.

Three cases of valproate-induced dyskinesia reported in association with significant learning difficulties.

1995. Early brain damage, poor frontal lobe function, and craniofacial dysmorphogenesis have been reported as possible risk factors by various authors.

In a study of outpatients aged over 45 years an increased of TD was associated with higher amounts of neuroleptics (esp. high potency), alcohol abuse/dependence, and subtle movement disorder at the start of the study.

1996. In first episode schizophrenia there was a cumulative incidence of presumptive TD of 6.3% after 1 year of follow up, 11.5% at 2 years, 13.7% at 3 years, and 17.5% at 4 years. The cumulative incidence of persistent TD was 4.8%, 7.2% and 15.6% at years 1, 2 and 4. Poor response to treatment and, to a lesser extent, antipsychotic drug dose, correlated with development of TD.

Schizophrenic patients who developed TD had larger left caudate nucleus on CT than those who did not develop this movement disorder.

Few British psychiatrists inform patients of risk of TD, often citing non-compliance as a reason.

Assessed dyskinesia in 4 groups of *elderly* Indians (normals, relatives of schizophrenics, never-medicated schizophrenics, and medicated schizophrenics): prevalence of dyskinesia similar in never-medicated and medicated patients (c 40%) and was significantly higher than in the other 2 groups (15%). Never-medicated schizophrenics had classic TD.

1997. A lack of the cytochrome P450 enzyme CYP 2D6 may contribute to the risk of neuroleptic drug-induced movement disorders, including TD; 5% of Caucasians have this deficiency (poor metabolisers); however, it does not make patients prone to acute dystonia.

In older patients, higher doses of neuroleptic, greater cumulative total neuroleptic dose, and greater severity of negative symptoms predicted severe TD – because of the lack of comparison with patients not on such drugs, spontaneous dyskinesia cannot be ruled out.

Nearly 15% of schizophrenic patients treated in the pre-neuroleptic era developed documented oro-facial movement disorders that were indistinguishable from TD. Being neuroleptic-naïve and schizophrenic carried a higher risk for movement disorder than having another diagnosis and being neuroleptic-naïve. Spontaneous dyskinesia, Parkinsonism, and neurological soft signs appear to represent neuromotor components of schizophrenia.

Association between Ser9Gly polymorphism in D3 receptor gene and TD.

Association between Taq 1 polymorphism in D2 receptor gene and TD (after chronic neuroleptic treatment).

Free radicals: lower blood or red cell superoxide dismutase (SOD) activity found in Parkinson's disease and Wilson's disease and in schizophrenic patients with TD: cause and effect unclear.

Never-treated schizophrenics in Morocco more commonly exhibit abnormal involuntary movements than do treated cases.

1998. 'Schizophrenia spectrum personality' (schizoid, paranoid, and schizotypal) v normals. No TD in latter. Spontaneous dyskinesia found in 12% of spectrum subjects, especially in schizotypals (24%).

Risk of developing TD is related to the number of interruptions in neuroleptic treatment (evidence against idea of 'targeted' or intermittent therapy).

Patients > 55 years of age getting neuroleptics for the first time: cumulative TD rates were 25%, 34%, and 53% after 1, 2 and 3 years of treatment (much higher than for young people, despite lower doses); risk increased with past ECT, higher mean daily and cumulative antipsychotic drug doses, and early EPS; and no difference between diagnostic groups in TD rates.

It is pointed out that EPS are reported in 17-29% of neuroleptic-naïve schizophrenics, raising the question of the role of antipsychotics in the aetiology of TD.

1999. The presence of a serine allele on D3 receptor might be a risk factor for TD.

Patients on olanzapine for over 200 days get TD but significantly less often than if on haloperidol for similar length of time.

Gabapentin improved TD in patients with mood disorders.(Hardoy ea, 1999)

Olanzapine may suppress respiratory dyskinesia.

2000. Increased incidence of TD (23% to 41%) in Nithsdale (Scotland) between 1981-96 might be due to greater use of antipsychotic drugs or intermittent compliance (increase in tremor by the same percentage as for TD).

Functional polymorphism in promotor region of CYP1A2 associated with TD.

2001. First episode and chronic schizophrenic patients (plus healthy controls) on typical agents; first episode cases put on risperidone and rescanned after a year (MRI); found no abnormalities; movement disorders seen in both groups of patients, suggesting effects of both illness and treatment.

Computerised neurocognitive tasks suggest orofacial TD and evident negative symptoms are relatively independent markers of compromise of cerebral systems mediating spatial working memory: fronto-striatal-thalamic systems, especially those involving DLPFC, may be involved.

Positive association between 5-HT 2C receptor gene and TD.

Positive association between 5-HT 2A receptor gene and TD.

Negative association between 5-HT 2A receptor gene and TD.

2003. Indian study finds that dyskinesia (but not Parkinsonism) is more common in never-treated siblings of schizophrenics who have the (corresponding) movement disorder. (McCreadie ea, 2003)

2004. Systematic review of 11 longterm studies suggest that risk for TD is less with second-generation antipsychotics compared to older agents, although doses of haloperidol in comparator studies were relatively high.

2006. Association of TD and EPS significant but do not robustly identify people at high risk for TD.

Abnormal Involuntary Movement Scale (AIMS)

1. Observe gait on way into room.
2. Have patient remove gum or ill-fitting dentures.
3. Check if patient aware of any movements.
4. Patient sits on firm armless chair, hands on knees, legs slightly apart, feet flat on floor – now and throughout examination observe entire body.
5. Patient sits with hands unsupported and dangling over knees.
6. Patient to open mouth twice – observe for tongue movements.
7. Patient to protrude tongue twice.
8. Patient taps thumb against each finger for 15 seconds with each hand – observe face and legs.
9. Patient stands with arms extended forward.

Rate each item on a 0-4 scale for highest severity observed. Movements that occur only on activation merit 1 point less than spontaneous movements.

0 = no movement, 1 = minimal (may be extreme normal), 2 = mild, 3 = moderate, and 4 = severe.

Facial + oral movements	1. Muscles of facial expression	0-4
	2. Lips & perioral area	0-4
	3. Jaw	0-4
	4. Tongue	0-4
Extremity movements	5. Upper	0-4
	6. Lower	0-4
Trunk movements	7. Neck/shoulders/hips	0-4
Global judgements	8. Severity of abnormal movements	0-4
	9. Incapacitation from abnormal movements	0-4
	10. Awareness* of abnormal movements	0-4**

*Patient's awareness. **0 = unaware, 4 = severe distress.

'Atypical' antipsychotic drugs (Kupfer & Sartorius, 2002)

Tandon (2004) defined atypical antipsychotic drugs as those that produced the same reduction in positive symptoms as did typicals but with less EPS (Lencer ea, 2004); they also cause less dysphoria, less TD, less negative symptoms, and better cognition³⁷⁶⁰. However, not all research agrees that changing from typical to atypical antipsychotic drugs improves quality of life (Jones ea, 2006), reduces discontinuation rates (Kuhn ea, 2008), is associated with less EPS (Miller ea, 2008) or is associated with increased effectiveness (Kuhn ea, 2008), and there is an argument that the concept of atypicality is unwarranted (Lieberman ea, 2005; Owens, 2008; Rosenheck, 2008; Leucht ea, 2009c) and that the atypical group is a heterogenous one (Leucht ea, 2009a). Neither is there agreement that atypical drugs are necessarily better than haloperidol in terms of cognitive improvement. (Davidson ea, 2009)

³⁷⁶⁰ Cognitive deficits predict functional outcomes. (Velligan, 2004)

It is thought that combined 5-HT₂ and D₂ receptor antagonism³⁷⁶¹ selectively enhances prefrontal DA activity, leading to correction of regional imbalance between cortical and midbrain dopaminergic systems. Actions on serotonergic systems may underlie improved profiles among atypical agents³⁷⁶², such as improvement in negative symptoms, although whether these drugs tackle primary or secondary negativity (e.g. Parkinsonism) is still debated. (Owens, 1998; Fleischhacker, 1999; Kopelowicz et al, 2000; Kane et al, 2001; Tandon et al, 2008) Kelsey et al (2007, p. 368) suggest that atypical agents cause less DA-blockade-associated side effects because (1) 5-HT₂ blockade attenuates effects of nigrostriatal DA blockade, (2) preference for D₄ blockade over D₂ blockade decreases degree of nigrostriatal/tuberoinfundibular DA blockade, and (3), at therapeutic doses, they occupy less (65-75%) of D₂ receptors than do typical antipsychotics. Alternatively, atypicals block D₂ receptors for relatively brief periods as with clozapine or (in the case of aripiprazole) act as partial agonists at D₂ receptors. PET work (Kegeles et al, 2010) seriously questions the mesolimbic selectivity of atypical antipsychotic drugs. There is no reason why atypicals *per se*³⁷⁶³ should not be used to treat mania, despite occasional reports that they cause mania³⁷⁶⁴. (Allen, 1998; Fahy & Fahy, 2000; Murphy, 2003; Hirschfeld et al, 2004) Concomitant use of a mood-stabiliser may or may not be necessary in such cases. One study suggested that risperidone plus a mood stabiliser was more efficacious than a mood stabiliser alone, and as efficacious as haloperidol plus a mood stabiliser for rapid control of mania. (Sachs et al, 2002) Tohen et al (2003) found olanzapine to be equal to haloperidol in terms of efficacy in treating bipolar mania; predictably, the former drug caused weight gain and the latter drug was associated with EPS.

Clozapine aside, the clinician would do well to choose an antipsychotic drug on the basis of its pharmacological and side-effect profile rather than whether it belongs to the novel/atypical/second generation or is an old/typical/first generation compound. (Bonham & Abbott, 2008; Crossley et al, 2010) The 'atypical' antipsychotic drugs are expensive. (Thomas & Lewis, 1998) While a meta-analysis of randomised controlled trials (RCTs) found clozapine better than conventional antipsychotic drugs for both treatment-resistant and non-resistant schizophrenia trials were mostly of short duration. (Wahlbeck et al, 1999) Moncrieff (2003) examined ten trials involving clozapine and found that recent large-scale studies did not find a strong clinical superiority for clozapine; shorter duration of study, pharmaceutical company backing, and higher baseline symptom score consistently predicted greater advantage for clozapine. Geddes et al (2000) conclude that when the dose of typical drugs is controlled for they are as efficacious and as tolerable as the atypical antipsychotics.³⁷⁶⁵ Chakos et al (2001) concluded that clozapine was more effective than typical drugs, but probably not by a robust margin, and the evidence, they found, was inconclusive for other new agents. In contrast, Azorin et al (2001) found clozapine superior to risperidone in previously poor treatment responders; both drugs were well tolerated, although clozapine caused less EPS. Volavka et al (2002) found clozapine, olanzapine and risperidone to cause statistically significant improvements on the PANSS relative to haloperidol, but results were clinically modest and the atypicals caused weight gain. Clozapine was best at reducing negative

³⁷⁶¹ When ritanserin, a specific central 5-HT₂ antagonist, was combined with a D₂ antagonist the result was a reduction in negative symptoms of schizophrenia and less EPS than would have been predicted from a D₂ blocking agent given alone. (O'Shea, 1998) Fananserin, a mixed D₄-5HT_{2A} antagonist, is not an antipsychotic. (Truffinet et al, 1999)

³⁷⁶² However, typical antipsychotic drugs like chlorpromazine also block 5-HT_{2A} receptors! (Trichard et al, 1998)

³⁷⁶³ Olanzapine, clozapine, sertindole, quetiapine, amisulpride, and ziprasidone. Sulpiride, remoxipride, and loxapine could be included in this list on the basis of low EPS potential. Whether amisulpride should be included depends on the definition. Mortimer (2002) stated that the most powerful predictor of 'atypicality' is fast dissociation of the drug from D₂ receptors: as measured by the K_{off}, clozapine and quetiapine have the fastest dissociation. A more satisfactory term is 'novel' antipsychotics, but this would omit clozapine. A scientific definition of an atypical antipsychotic drug is that (unlike typical drugs) it *doesn't cause catalepsy in rats*. In real-life clinical practice, there is only one sure way of knowing who will respond to a particular drug, and that means trying it. Some patients for example respond to risperidone and not to clozapine and *vice versa*. (Bondolfi et al, 1998)

³⁷⁶⁴ Vieta et al (2004) found that risperidone exacerbated mania in 4.2% of cases of mania.

³⁷⁶⁵ Interestingly, the authors included clozapine in the typical group!

symptom scores. Davis ea, (2003) in a meta-analytic study, found that clozapine, amisulpride, risperidone and olanzapine³⁷⁶⁶ were more efficacious than first-generation antipsychotics. Unlike Geddes ea, (2000) Davis ea (2003) did not find that the dose of haloperidol or other first-generation antipsychotics affected these results, and the latter authors found no difference in efficacy between amisulpride, risperidone and olanzapine. Sechter ea (2003) found a similar efficacy between amisulpride and risperidone in chronic schizophrenia; both drugs had a similar incidence of EPS, but amisulpride had less endocrine and sexual adverse effects and caused less weight gain. McCue ea (2006) found haloperidol, olanzapine, and risperidone superior to aripiprazole, quetiapine, and ziprasidone in the treatment of acute schizophrenia. Robinson ea (2006) used olanzapine or risperidone for first-episode schizophrenia: clinical outcomes were equal and olanzapine caused less motor side effects but caused more weight gain. Leucht ea (2009b) analysed 78 studies of schizophrenia patients and found olanzapine superior to aripiprazole, quetiapine, risperidone, and ziprasidone; risperidone was better than quetiapine and ziprasidone; clozapine was superior to zotepine and (if dose was > 400 mg/day) risperidone; such differences as there were derived from reduction in positive but not negative symptoms. The authors stated that results 'were rather robust' in relation to the influence of pharmaceutical industry sponsorship, the quality of research, doses, and duration of trials! Komossa ea (2009) reviewed RCTs and concluded that aripiprazole was somewhat less effective than olanzapine although aripiprazole had less sedative and metabolic side-effects than olanzapine; risperidone and aripiprazole may be equally efficacious but aripiprazole was less likely to cause dystonia, increased cholesterol and prolactin, and had less effect on QTc.

Despite some methodological deficiencies, research indicates that atypical antipsychotic drugs help to prevent relapse in schizophrenia.(Leucht ea, 2003)

Sertindole and clozapine, and probably quetiapine, do not increase prolactin levels, at least not in any clinically significant manner.(cf. Turrone ea, 2002)

The risk for dysglycaemia is doubled in community-based treated schizophrenic patients compared to the general population, and recognition and treatment of diabetes and pre-diabetes is low in this group.(Voruganti ea, 2007) As pointed out by Leonard ea,(2002) the role of clozapine³⁷⁶⁷ is unclear because high rates of diabetes were reported in schizophrenia before the advent of any antipsychotic drugs (Mukherjee ea, 1996) and atypical antipsychotics (Dixon ea, 2000), obesity is common in schizophrenia (Taylor & McAskill, 2000), and the prevalence of obesity generally may be increasing.(Murphy, 2001) Also, impaired fasting glucose tolerance has been reported in drug-naïve, first-episode schizophrenics.(Ryan ea, 2003) Also, beta-cell function and insulin sensitivity have been found to be inversely correlated with acute psychotic stress.(Shiloah ea, 2003) Nevertheless, BMI results do tend to implicate clozapine.(Leonard ea, 2002) Hedenmalm ea (2002) reported increased risk of glucose tolerance in patients on clozapine, olanzapine, or risperidone. In a prospective randomised study, Lindenmayer ea (2003) found that clozapine, olanzapine, and haloperidol were associated with increased plasma glucose values, and the two atypicals were associated with increased plasma cholesterol levels. Elevated serum triglyceride levels has been recorded in patients taking phenothiazines, clozapine, olanzapine, and quetiapine.(Farmer, 2003) Use of atypical antipsychotic drugs in children and adolescents may lead to obesity and abnormal metabolic parameters, with olanzapine (worst) and aripiprazole (best among the drugs studied) being at opposites extremes.(Correll ea, 2009)

What are the issues involved in the employment of atypical drugs to control behavioural and psychiatric symptoms in people with dementia? This issue is discussed below with regard to individual drugs. Some general issues are covered here. The *en masse* withdrawal of these drugs that followed warnings of increased (about threefold from

³⁷⁶⁶ But not aripiprazole, quetiapine, remoxepriide, sertindole, ziprasidone, or zotepine. Zotepine was 'marginally different' from first-generation agents.

³⁷⁶⁷ Or other neuroleptics *per se* for that matter.

1.1% to 3.3%) risk for cerebrovascular incidents has been condemned as being hasty. Individual patient circumstances and the side effect profile of alternatives should come first, i.e. a risk-benefit analysis should have been performed (see Haw ea, 2009). Herrmann ea (2004) and Gill ea (2005) found no excess of cerebrovascular incidents in elderly people given atypicals compared to those given typical antipsychotics, but Gill ea (2007) did find early increase in mortality (typical > atypical antipsychotics). Mehta ea (2010) conducted a retrospective study of community-dwelling older adults and found that second generation antipsychotic agents were associated with an increased risk of cerebrovascular incidents compared to first generation drugs and that long-term use of either of these classes of drug were associated with an increased risk of such adverse events. Douglas and Smeeth (2008) looked at a UK general practice database and found that use of any antipsychotic drug was associated with a rate ratio for stroke of 1.73 for typicals and 2.23 for atypicals; in patients receiving any antipsychotic drug the rate ratios were 3.50 for dementia patients and 1.41 for non-dementia patients. There is more research evidence for the effectiveness of atypical drugs in managing behavioural and psychiatric symptoms in people with dementia than for the typical drugs. Patients should only be retained on these drugs (after due consultation) if they have responded to them, if the behavioural problem is persistent or if severe adverse consequences are likely to follow their discontinuation, or if no suitable alternatives exist. It is good practice, however, to keep such prescribing under review (say, every 3 months) and to document why a decision is made. Also, if adverse effects become burdensome (as often happens), the clinician may need to withdraw the medication or modify the dosing regimen.(Schneider ea, 2006)

Atypical antipsychotic drugs (O'Shea, 1998)

Clozapine³⁷⁶⁸ (Clozaril, Denzapine: a dibenzazepine): Despite nine Finnish deaths from clozapine-induced agranulocytosis during the 1970s, interest in clozapine was resurrected by Kane ea (1988) who found that after 6 weeks 30% of treatment-resistant schizophrenic patients responded to clozapine³⁷⁶⁹, only 4% to a typical agent. Clozapine is indicated for nonresponse to or intolerance to other antipsychotics and for treatment of unresponsive psychosis in Parkinson's disease.

Clozapine is said to improve both positive and negative symptoms of schizophrenia, although some results suggest that such negative symptoms may actually represent withdrawal responses to positive symptoms, and not all results agree that negative symptoms are helped.(Buchanan ea, 1998; Breier ea, 1999) It is indicated for schizophrenic psychosis refractory to adequate trials of (2 to 3) other drugs or where side effects prohibit the use of other drugs. It is thought to improve 30-50% of patients in the former category and 70-76% in the latter group. Not every patient will respond to clozapine.(King & Mills, 1993) Early onset of illness and female sex may be indicators of poor response.(Lieberman ea, 1994) There is a greatly reduced³⁷⁷⁰ risk of TD and it may actually improve established TD.

Possible reasons for lack of neurological adverse effects of clozapine

Potent anticholinergic action

Preferential binding: limbic > striatum

³⁷⁶⁸ 5-H dibenzo [be, e]-1, 4-diazepine; synthesised in 1958; found effective for schizophrenia in 1962; originally developed by Hünziker and co-workers. Granulocytopenia due to clozapine was reported in 1975. Ashkenazi Jews and Finns may be at special risk of agranulocytosis from clozapine. Clozapine-induced agranulocytosis usually reverses in 2-3 weeks after stopping the offending drug. Also, it should be noted that Walker ea (1997), using the US Clozapine National Registry, found that stopping clozapine was associated with a higher mortality rate than was staying on the drug; this was mainly due to clozapine's effect of reducing suicide risk.

³⁷⁶⁹ Reasons for clozapine's efficacy in resistant cases may relate to its complex receptor profile or to the fact that it is less dependent than are other neuroleptics on P-glycoprotein, a drug efflux transporter, in order to traverse the blood-brain barrier.(Loscher & Potschka, 2005)

³⁷⁷⁰ Clozapine carries the lowest risk of all antipsychotics for TD, but the absence of risk is not absolute.(Dave, 1994)

High D2 dissociation constant ³⁷⁷¹ 5-HT2A antagonism

Fluoxetine may increase clozapine levels. ECT is usually safe with clozapine (prolonged seizure is rare). Clozapine may reduce hostility and suicidality, but not all reports agree. It may be useful for L-DOPA-induced dyskinesia and for psychosis in Parkinson's disease, in which clozapine is well tolerated³⁷⁷². Polydipsia may be diminished by clozapine therapy. Among the other reported indications for clozapine are treatment-refractory mania, psychotic depression, and schizoaffective disorder. High doses may suppress chorea in Huntington's disease. A more controversial suggestion is its use for intractable borderline personality disorder.

The starting dose is 12.5mg once/twice daily, increasing slowly to 300 mg within 2-3 weeks, and the usual effective dose is 200-450 mg/day. Optimum (best response/least adverse effects) trough (blood drawn at end of dosing interval) plasma clozapine levels are 0.35-0.6 mg/L.(Flanagan, 2007) Fluvoxamine should be avoided as it increases clozapine levels or the clozapine level might need halving if the combination is employed. Deaths have followed cessation of smoking because of increased clozapine levels³⁷⁷³.

Clozapine pharmacokinetics in children and adolescents differs from those in adults: levels of the active metabolite norclozapine are up to 25% less than those of clozapine in adults, whereas younger patients have higher norclozapine than Clozapine levels. Adverse effects vary with norclozapine levels, therapeutic effects varying with levels of Clozapine.(James & McClellan, 2008, p. 824)

Clozapine is considered to have relatively weak antidopaminergic actions³⁷⁷⁴ but to strongly block 5-HT2 receptors³⁷⁷⁵, to have high affinity for D4³⁷⁷⁶, 5-HT6 and 5-HT7 receptors, to have strong actions at alpha-1 (postsynaptic) and alpha-2 receptors. 5-HT antagonism may be relevant to clozapine's efficacy against positive symptoms³⁷⁷⁷,(Jones ea, 1998) although one small SPECT study failed to find any relationship between 5-HT2A receptor blockade by either clozapine or risperidone and global outcome in schizophrenia.(Travis ea, 1998) Interestingly, monotherapy with a HT2A receptor blocking drug (e.g. M-100907) does not seem to be effective in schizophrenia.(Miyamoto ea, 2003, p. 452) When the potent alpha-2 antagonist idazoxan is added to fluphenazine it may improve the therapeutic activity of the latter drug, which suggests that one cannot rule out alpha-2 antagonism as a possible antipsychotic mechanism for clozapine. SPECT has shown future clozapine responders to have a relatively high perfusion of the thalamus, left basal ganglia and right prefrontal regions whilst on prior neuroleptic treatment, subcortical perfusion decreasing when a good response was achieved to clozapine. Prepulse inhibition is reduced in schizophrenia.³⁷⁷⁸ Clozapine appears to normalise prepulse inhibition to a greater degree than do conventional antipsychotics in schizophrenia. Clozapine may be more efficacious than typical antipsychotic drugs in

³⁷⁷¹ It binds loosely to D2 receptors.

³⁷⁷² Use low doses: start with 12.5 mg/day and increase slowly in Parkinson's disease, the maximum dose being 100 mg/day, although the usual effective dose is usually 25-37.5 mg/day.

³⁷⁷³ Nicotine patches do not affect clozapine levels. Starting to smoke leads to a fall in clozapine levels, as when patients leave smoke-free inpatient units. The effect from nicotine and cannabis cigarettes on clozapine levels may be due to hydrocarbons.(Flanagan, 2007)

³⁷⁷⁴ Low D2 occupancy in basal ganglia may explain low EPS; D2 and D3 blockade in temporal cortex is similar to typical drugs;(Pilowsky ea, 1997) but PET data suggests low D2 occupancy in both striatum and extrastriatal regions.(Talvik ea, 2001)

³⁷⁷⁵ Homozygosity of C102 allele in coding region of 5-HT2A gene on chromosome 13q was at first considered more common in non-responders but further work found no relation between allelic variation in this gene and response to clozapine.

³⁷⁷⁶ Whether this explains its antipsychotic action is doubtful because the distribution of alleles for the D4 gene does not distinguish responders from non-responders.(see Shaikh ea, 1993) High dose chlorpromazine also blocks 5-HT2A receptors.(Trichard ea, 1998)

³⁷⁷⁷ Blunted prolactin response to d-fenfluramine at 20 months correlated with reduction in positive symptoms.

³⁷⁷⁸ Prepulse inhibition means a reduction in response to a strong startle stimulus if this is preceded by [30-50 msec] a prestimulus or prepulse that is too weak to cause a measurable startle response itself; prepulse inhibition is regulated by forebrain cortico-striato-pallido-thalamic-mediated plasticity (gating) of the startle response. The results of a study (Perry ea, 2002) suggested that prepulse inhibition is abnormal in acute psychotic schizophrenia independent of medication status.

reducing comorbid substance abuse in schizophrenia: 50% of schizophrenics abuse substances at some time (e.g. cocaine), often as self-treatment.(Buckley, 1998) The plasma half-life of clozapine is 6-26 hours (mean = 12 hours)³⁷⁷⁹. It is subject to first-pass metabolism. The absolute bioavailability is 50-60%. 95% is bound to plasma protein. Inactive metabolites are excreted in urine (50%) and faeces (30%). It may compete with warfarin for protein binding sites. Clozapine does not induce catalepsy or block stereotypies induced by DA agonists, or, after chronic treatment, produce DA receptor supersensitivity. Clozapine can cause neutropaenia and agranulocytosis³⁷⁸⁰, especially during the first 6 months of therapy³⁷⁸¹, in the elderly, and in females. Asians may be at increased risk of agranulocytosis. Granulocyte colony-stimulating factor may normalise clozapine-induced neutropaenia. Clozapine's anticholinergic effects may potentially compromise cognitive function in some patients (Goldberg ea, 1993) although it is suggested also that clozapine ameliorates cognitive dysfunction, especially attentional and verbal fluidity problems, in schizophrenia.

Treatment is initiated and monitored in co-operation with the manufacturers (Clozaril Patient Monitoring Service - CPMS).³⁷⁸² Monitoring is less in some countries than others.(e.g. Tharyan, 1998) Clozapine should not be given if there is a history of agranulocytosis and it should not be combined with other drugs capable of inducing agranulocytosis³⁷⁸³, e.g. carbamazepine, propylthiouracil, captopril, or sulphonamides (with the exception of previous chemotherapy). The use of depot antipsychotic drugs is discouraged. The cumulative incidence of agranulocytosis during one year of exposure is 0.8%. Fatal agranulocytosis occurs in 0.01% of patients monitored by the CPMS and in 0.3% of those not monitored. According to Atkin ea,(1996) after 4.5 years (n = 6,316 patients in UK and Ireland) 2.9% of patients developed neutropaenia and, again, 0.8% had developed agranulocytosis. The first 6-18 weeks of treatment contained the peak incidence of both disorders. Fatal agranulocytosis occurred in 0.03% of patients, the incidence of agranulocytosis showing a decrease to that noted with some phenothiazines. Figures from the CPMS in February 2003 showed an incidence of agranulocytosis per 1000,000 person-weeks of observation of 32.0, 2.3 and 1.8 for weeks 0-18, 19-52 and 53 onwards respectively. Rosenheck ea (1997) reported that 3 out of 205 patients on clozapine developed agranulocytosis, all showing full recovery. Mild/moderate neutropaenia (500-1500 neutrophils/cu mm) rapidly reverses on cessation of clozapine. Severe neutropaenia (less than 500 neutrophils/cu mm), mild asymptomatic eosinophilia, chronic leucocytosis (sometimes with low-grade pyrexia), and severe lymphopaenia (with/without fever and diarrhoea) may also occur. Clozapine should be stopped immediately if the WCC (WBC) is below 3000/cu mm or the absolute neutrophil count (ANC) is below 1500/cu mm. If the WCC is 3000-3500 or the ANC is 1500-2000 the clozapine is continued with twice weekly blood sampling until the counts stabilise or increase. Values of at least 3500 and 2000 for WCC and ANC respectively indicate that clozapine therapy can continue. Clozaril should be discontinued if the eosinophil count rises over 3000/cu mm, and only restarted after it falls below 1000. The same applies if the platelet count falls below 50000/cu mm.

In the UK and Ireland, a WCC (white cell count) with differential count is done weekly for 18 weeks, two-weekly for weeks 18-52, and thereafter every 4 weeks. Monitoring should continue for at least 4 weeks after stopping clozapine. In the US, weekly WBC (white blood cell count) and ANC (absolute neutrophil count) are required for the first 6

³⁷⁷⁹ The main metabolite is norclozapine, which appears to be active and to have a longer half-life than clozapine. The clozapine/norclozapine ratio is important. Norclozapine levels are less prone to fluctuation and give a better idea of compliance.

³⁷⁸⁰ Agranolcytosis in 1% of cases.

³⁷⁸¹ A number of experts question the need for continued white cell monitoring beyond that point.

³⁷⁸² The clozapine generic preparation **denzapine** (Merz Pharma) became available in 2010. A web-based Denzapine Monitoring System (DMS) allows secure access to patients' blood monitoring and dispensing history and support from trained staff including an on-call haematologist.

³⁷⁸³ Ghaznavi ea (2008) argue that causes of neutropaenia other than clozapine should be sought and that consideration should be given to tapering the (assumed) offending drug first before stopping clozapine.

months (and for 4 weeks after stopping clozapine), every 2 weeks from 6-12 months, and every 4 weeks thereafter.

Re-challenge with clozapine following significant leucopaenia or neutropaenia is contraindicated. However, it has been done. Dunk ea (2006) re-challenged 56 patients. 20 experienced further blood dyscrasia of whom 20 experienced a more severe dyscrasia and in 12 it was of longer duration. In 17 of the 20 experiencing dyscrasia haematological problems occurred more quickly than had on first exposure to the drug. The authors concluded that re-challenge may be justified in some cases. Of course, potential benefits would have to be greater than the risks of re-challenge and wide consultation would be mandatory.

Some side effects of clozapine³⁷⁸⁴

Sedation³⁷⁸⁵

Ptyalism (especially nocturnal),³⁷⁸⁶ dry mouth, nausea, vomiting, weight increase (with risk of diabetes)³⁷⁸⁷

Increases in liver enzymes, cholestasis, hypertriglyceridaemia, obesity, hypertension (e.g. Feeney ea, 2007)

Dizziness

Constipation³⁷⁸⁸

Tachycardia,³⁷⁸⁹ cardiac arrhythmias, prolongation of the QT interval,(Cohen ea, 2001) heart block, pericarditis, myocarditis,³⁷⁹⁰ thromboembolism (*keep the patient mobile*) (O'Lunaigh & Scully, 2006)

Postural hypotension (see below), hypertension

Respiratory depression

Transient pyrexia³⁷⁹¹

Skin rashes

Tremor, akathisia, rigidity, seizures³⁷⁹²

Stuttering (Hallahan ea, 2007)³⁷⁹³

Urinary incontinence

Clozapine should not be given to people with (rare) inherited problems of galactose intolerance. Uncontrolled epilepsy is a contraindication to clozapine therapy, as are severe liver dysfunction or paralytic ileus. Orthostatic hypotension, excess sedation or confusion should prompt a limitation/deferment of dose increases; for very severe cases of postural hypotension, moclobemide and Bovril have been used (Goldberg, 1997) but do not use adrenaline because clozapine's (and other antipsychotics with similar actions) anti-adrenergic effect may lead to a reverse effect from adrenaline with a further fall in blood pressure.

The risk of myocarditis³⁷⁹⁴ is greatest in the first 6-8 weeks of treatment. If the diagnosis is confirmed, re-challenge with clozapine is contraindicated.

³⁷⁸⁴ Different protocols suggest monitoring different things and at different frequencies, e.g. serum troponin during the first 8 weeks and lipids and fasting blood glucose 6-monthly or more frequently.

³⁷⁸⁵ Often for first 4 weeks; made worse by alcohol; may respond to modafinil.

³⁷⁸⁶ Drooling/sialorrhoea/hypersalivation: this is unexpected considering clozapine's anticholinergic activity but may relate to impaired oesophageal motility. Anticholinergic drugs, hyoscine, propantheline, pirenzepine, amisulpride or clonidine are suggested remedies.

³⁷⁸⁷ 36.8% developed diabetes in one five-year follow-up. Lund ea (2001) found no greater risk of diabetes or hyperlipidaemia than with conventional agents, but Newcomer ea (2002) have shown that clozapine is associated with hyperglycaemia.

³⁷⁸⁸ High fibre diet or bulk-forming laxatives may be required.

³⁷⁸⁹ If very severe consider low dose β -blocker.

³⁷⁹⁰ Rare (0.015-0.188%); may be fatal, with eosinophilic infiltration and myocytolysis.(Coulter ea, 2001)

³⁷⁹¹ This usually occurs during the first few weeks of treatment and lasts a few days.

³⁷⁹² Lipid and seizure disorders can occur in clozapine-treated children and adolescents.(Shaw ea, 2006)

³⁷⁹³ Cases have responded to dose reduction and, if related to seizures, sodium valproate.

³⁷⁹⁴ The risk of myocarditis from clozapine is at least 0.015-0.188%, although it has been suggested that up to 66% may have some non-specific findings consistent with this diagnosis.(Merrill ea, 2006) Suspect myocarditis or cardiomyopathy if there is persistent

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Pseudophaeochromocytoma³⁷⁹⁵ has been described in a number of cases receiving clozapine therapy. Management includes stopping clozapine. (Prasad & Kennedy, 2003) Seizures are especially common in high dose regimes: one estimate is that 1-2% experience seizures at doses up to 300 mg/day and 5% at 600-900 mg/day and another estimate is that 10% of patients after 3.8 years of clozapine treatment had experienced seizures. Phenytoin can decrease clozapine levels and compromise bone marrow status. The prescriber should use valproate³⁷⁹⁶ or phenobarbitone for seizures when necessary. Clozapine should be withheld for 24 hours after a seizure and restarted at a lower dose. Clozapine may potentiate the effects of alcohol, BZDs³⁷⁹⁷ and other central depressants, MAOIs and hypotensive drugs. Combination with BZDs, not uncommon in practice, may cause excess sedation, loss of consciousness, respiratory distress, and lability of blood pressure; the advice is to titrate doses slowly. (Chong & Remington, 2000; Travis, 2002) Rebound psychosis (and cholinergic rebound) may follow withdrawal of clozapine: do not interrupt clozapine on admission to a general ward; if it is stopped for over 4 days it should be reintroduced at a low dose and titrated up to the original dose. Prolactin levels remain normal. Pregnancy and breastfeeding are contraindications to clozapine. Contraceptive measures may be needed (if menses return). Careful monitoring is essential in the presence of liver disease. NMS may be more likely if lithium is co-prescribed with clozapine. Do not give clozapine with depot antipsychotics³⁷⁹⁸. Outrule an immunocompromised state before starting clozapine, e.g. TB or HIV. Great care is required in those patients with prostatic enlargement, narrow angle glaucoma or paralytic ileus. Clozapine may exacerbate obsessions and compulsions³⁷⁹⁹.

Overdose³⁸⁰⁰

Mortality c. 12%

Death chiefly from cardiac failure or aspiration pneumonia

MacGillivray *et al.* (2003) conducted a retrospective study of 201 people who commenced clozapine therapy between 1990 and 1997. Of these, 45% had discontinued clozapine before 3 years. The latter were more likely to have been relatively elderly at the start of therapy with this drug. Despite the number of potentially serious complications, clozapine may reduce the net mortality rate, possibly by reducing the suicide rate. (Walker *et al.*, 1997)

Risperidone³⁸⁰¹ (Risperdal; Quicklet orodispersible tablets in 1 mg and 2 mg strengths; liquid = 1 mg/ml; Risperger, Rispal) is a benzisoxazole derivative with a half-life of four hours. (Edwards, 1994) The metabolite 9-hydroxyrisperidone is active and has a half-life of 22 hours (see paliperidone). The combined active moiety has a half-life of 24 hours. Risperidone is a potent 5-HT₂ and D₂ antagonist (PET suggests equal D₂ occupancy as for low dose typical and risperidone has a low dissociation constant for D₂ receptors, i.e. it sticks tenaciously to the receptor) that is devoid of central anti-Ach activity. EPS is only important at higher doses. (e.g. Marder *et al.*, 2003) A single dose of risperidone reduces glucose metabolism in the ventral striatum, thalamus and frontal cortex, and the

tachycardia at rest, palpitations, arrhythmias, chest pain, other signs of heart failure, or symptoms suggestive of myocardial infarction. Such patients should stop taking clozapine and see a cardiologist.

³⁷⁹⁵ Hypertension, tachycardia and elevated 24-hour urinary catecholamines.

³⁷⁹⁶ Which can increase clozapine levels.

³⁷⁹⁷ Probably safe in most cases once stable clozapine dosage is achieved.

³⁷⁹⁸ Increased risk of neutropaenia.

³⁷⁹⁹ This may be a result of antagonism at 5-HT₂ receptors or it may be associated with sequence variations in the glutamate transporter gene SLC1A1. (Kwon *et al.*, 2009) SSRIs are usually effective.

³⁸⁰⁰ Overdose leads to a drowsy, lethargic, areflexic or hyperreflexic, confused, hallucinated, agitated, delirious state. There may be coma. Extrapyramidal signs, seizures, hypersalivation, big pupils, cycloplegia, labile temperature, hypotension, tachycardia, cardiac arrhythmia, and dyspnoea may be found. Management involves gastric lavage with or without activated charcoal if the time since ingestion is less than six hours. Avoid adrenaline. Treat symptoms and monitor organ function and electrolyte levels and acid-base balance. Delayed reactions should be considered during the first week.

³⁸⁰¹ Like haloperidol, risperidone was synthesised by Paul Janssen.

degree of reduced metabolism in the left hippocampus may predict amelioration of positive symptoms. It lacks disturbing levels of sedation. Working memory may be improved in risperidone-treated schizophrenic patients compared to those patients receiving haloperidol or, according to Bilder *et al.*, (2002) even clozapine. There is evidence from a double-blind multicentre prospective trial that risperidone is superior to haloperidol in reducing the risk of relapse in clinically stable outpatient schizophrenic and schizoaffective patients. (Csernansky *et al.*, 2002) Risperidone has alpha-1 and alpha-2 adrenergic and histamine receptor blocking actions. Metabolism is via hydroxylation and N-dealkylation. Peak plasma concentration is reached in 1-2 hours. 88% is plasma protein bound, as is 77% of its metabolite. Steady state serum levels are reached within 5 days. Prolactin levels are increased. It has been suggested that raising the prolactin level (as a measure of DA blockade) up to about 20 may allow maximum antipsychotic effect with minimum EPS. (Williams, 1999) Initial hyperprolactinaemia in children tends to decrease over time. (James & McClellan, 2008, p. 824) Concentrations of risperidone in breast milk are similar to those in serum but placental transfer is limited. Risperidone is excreted in faeces and urine. The starting dose is 0.5-1 mg bid, the lower dose being appropriate in the elderly or in people with renal or hepatic disease. Doses over 5 mgs bid probably give no increase in efficacy, and the optimal dose may be c 6 mg/day.³⁸⁰² EPS becomes more likely as dose increases. The liquid form contains 1 mg/ml.

Potential side effects

Anxiety, headache, somnolence (or insomnia), fatigue, dizziness, poor concentration
 Constipation, indigestion, nausea, abdominal pain
 Diplopia
 Erectile and ejaculatory dysfunction, orgasmic difficulties
 Rhinitis
 Skin rash
 EPS (incl. dystonia)
 Orthostatic hypotension with reflex tachycardia
 Galactorrhoea, amenorrhoea
 Weight gain (Sernyak *et al.* [2002] report a risk of diabetes in younger patients – cf. olanzapine next)
 Water intoxication (hyponatraemia)
 Seizures
 Nose bleeds, +/- thrombocytopenia (Harrison-Woolrych & Clark, 2004)
 Overdose: sedation, tachycardia, hypotension and EPS

Olfson *et al.* (2006) but not Koro *et al.* (2002) reported an increased risk for hyperlipidaemia in patients on risperidone. TD may be less likely than with typical drugs³⁸⁰³ and NMS appears to be very rare. (Kane, 1994) However, TD has been described in patients on risperidone. Transient hypertension could follow abrupt withdrawal of risperidone, possibly due to withdrawal of its alpha-1 blocking effect. Randomised trials in elderly demented patients suggest a threefold increase in cerebrovascular adverse events (3.3% v 1.2% in risperidone- and placebo-treated cases respectively). Patients should be monitored for any evidence of such events and consideration should be given to stopping the drug if necessary. This risk may be higher for patients with a past history of CVA/TIA, hypertension or cardiovascular disease. Of note is the finding of a systematic review of risperidone and olanzapine in demented patients (Lee *et al.*, 2004) that found adverse events to be common, i.e. EPS, somnolence, and gait abnormality. The trials

³⁸⁰² 4-8 mg dose range: bell-shaped dose-response curve. Perhaps the optimal D2/5-HT2A blocking ratio occurs in the 6-8 mg/day range. 4 mg/day has also been recommended as the ideal dose because it is associated with 70-80% D2 occupancy.

³⁸⁰³ There is some evidence that it may actually improve severe TD. (Chouinard *et al.*, 1993)

looked at were too short to pick up impaired glucose metabolism or hyperlipidaemia. CVA/TIA was not reported, possibly for the same reason.

Risperidone depot (Risperdal Consta – 25 mg, 37.5 mg, 50 mg) consists of risperidone microspheres (Medisorb) that gradually release medication. A SmartSite Vial Access Device offers needle-free access to the vial of microspheres, thus eliminating the original need for 3 needles. It is recommended that the drug be administered orally for three weeks *until therapeutic levels of the long-acting drug are achieved*, after which attempts are made to withdraw oral risperidone. However, oral supplementation may take longer in practice³⁸⁰⁴. (Paton & Okocha, 2004) The injection is then given every 2 weeks. (Imperio, 2001) The initial dose is 25 mg IM (*gluteal or deltoid*) two-weekly. 37.5 mg might be considered if the patient has been stable on over 4 mg per day. An increase in the initial dose of 12.5 mg can be considered after 4 weeks elapse (in fact 4 weeks interval is suggested between all dose increases). The maximum dose is 50 mg every 2 weeks. One naturalistic study of 50 patients found an attrition rate of 42% at six months. (Paton & Okocha, 2004) A randomised, controlled, open-label study (Keks ea, 2007) found depot risperidone and oral olanzapine to be equally efficacious. According to Turner ea (2004) a stable patient's conventional depot antipsychotic drug can be changed directly to Risperdal Consta without an intervening period on oral risperidone³⁸⁰⁵.

Paliperidone (Invega extended-release tablets³⁸⁰⁶) is the active metabolite of risperidone (9-hydroxyrisperidone). There is no need for dose titration³⁸⁰⁷. There is minimal hepatic metabolism of the drug. The drug occupies central D2³⁸⁰⁸ and 5-HT2A receptors³⁸⁰⁹. It may have an early onset of action. It is suggested that one-third of its effects on negative symptoms is attributable to a direct drug effect. It improves personal and social functioning and may have a relatively early therapeutic effect. (Canuso ea, 2009) Paliperidone, which appears to have a good 6-week metabolic profile, (Meyer ea, 2006) may increase prolactin levels³⁸¹⁰ and may cause akathisia and EPS (9 mg or above). There is a modest increase in QTc. NMS has been reported. Orthostatic hypotension and syncope may occur. Weight increase appears not to be a major issue. (Owen, 2007) Paliperidone should be avoided in demented psychotic patients. Caution is advised if there is a history of seizures.

Paliperidone palmitate long-acting injection is undergoing trials.

Olanzapine (Zyprexa oral tablets: 2.5, 5, 7.5, 10 and 15 mg), a thienobenzodiazepine and derivative of the clozapine molecule, is well tolerated relative to other antipsychotics. (Lieberman ea, 2005). It shows affinity for 5-HT2, D1, D2 and muscarinic receptors.³⁸¹¹ It seems less likely than typicals to cause EPS or TD³⁸¹² and much less likely to cause haematological problems than clozapine. It improves depression in schizophrenia more than does haloperidol³⁸¹³, although it was equally efficacious (but

³⁸⁰⁴ Some authorities give oral risperidone until the patient has received the third Consta injection. They also give oral risperidone for 3 or 4 weeks after an increase in Consta dosage. However, Risperdal Consta has been given to patients with schizophrenia or schizoaffective disorder (diagnosed within previous 3 years, symptomatically stable, on same dose of an antipsychotic for at least 1 month, open and non-comparative study) and was well accepted. (Parellada ea, 2005)

³⁸⁰⁵ One possible approach is to give a Risperdal Quicklet on day one and the depot next day if there is no adverse reaction.

³⁸⁰⁶ Uses osmotic-release oral system (OROS) to deliver drug in an extended-release formulation over 24 hours in order to minimise peak-trough fluctuations (once-daily dosing). According to Pani (2008) risperidone or even haloperidol would be improved by using the OROS system, i.e. there would be smoother plasma levels with less likelihood of the drug being in the higher, EPS-inducing range.

³⁸⁰⁷ The usual dose is 6 mg mane.

³⁸⁰⁸ Mean striatal D2 occupancy of 75-78% for a dose of 6 mg: <65% would be sub-therapeutic and >80% would increase risk for EPS.

³⁸⁰⁹ It should be noted that antagonism of 5-HT2A receptors in the striatum is thought to lead to release of dopamine.

³⁸¹⁰ Pani (2008) states that prolactin elevation induced by paliperidone is similar to that caused by risperidone.

³⁸¹¹ PET work suggests that near saturation of 5-HT2 receptors at only 5 mg/day and that D2 occupancy increases with increasing dose; the D2 occupancy is higher than that for clozapine but similar to that of risperidone. PET suggests equal D2 occupancy with olanzapine and risperidone as for low dose typicals.

³⁸¹² 7% got TD on olanzapine and 16.2% got TD on haloperidol after a median of just over 200 days in one study; a review suggested that there is no greater risk of TD than in never-medicated psychosis, i.e. '1% per year'.

³⁸¹³ Or does it cause it less often?

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with less adverse effects) with chlorpromazine for treatment-resistant schizophrenia in one study.(Conley ea, 1998) Patients with Parkinson's disease show limited tolerability for olanzapine. Cognitive function may be improved in olanzapine-treated schizophrenic patients, but probably by little more when compared with low doses of haloperidol or with other atypicals.(Keefe ea, 2004; Keefe ea, 2007)

Side effects

Common³⁸¹⁴

Somnolence

Weight gain (with risk of diabetes: Newcomer ea [2002], Koro ea [2002]; caloric intake is increased on olanzapine and schizophrenic patients take little exercise with or without this drug: Gothelf ea [2002]; adding fluoxetine does not help: Poyurovsky ea, [2002]; topiramate [Topamax], 50 mg/day is worth trying [Vieta ea, 2004])

Less common

Dizziness, peripheral oedema, postural hypotension, transient anticholinergic effects³⁸¹⁵, and raised liver transaminases³⁸¹⁶

Koro ea (2002) reported an increased risk for hyperlipidaemia

Rare

Photosensitivity

Elevated CPK

Asymptomatic blood changes

At least one case of priapism

Pancreatitis has been rarely reported, but alcohol probably played a role in those cases

ALT (SGPT) is raised in 2% of treated patients

Falanagan (2007) suggests that the therapeutic plasma level for olanzapine in a 10-16 hour post-dose sample is 23 µg/L. Smoking and carbamazepine induce activity in cytochrome P450 1A2 enzyme, increasing olanzapine metabolism. Clearance of olanzapine is 33% lower in non-smokers than in smokers. Carbamazepine increases olanzapine clearance by 44%. Prolactin increase can occur, but is often transient and asymptomatic. The starting dose is 2.5-10 mg, lower doses being used in the elderly or those with liver or kidney impairment. The usual dose range is 5-20 mg/day.

*Zyprexa VeloTabs*³⁸¹⁷ dissolve in the mouth and are a useful strategy in non-compliant acute cases.

Olanzapine (*Zyprexa IM*: 10 mg Powder for Solution for Injection) is a 'rapid acting intramuscular' preparation for use in the acutely agitated psychotic patient.(Jones, 2001) 10 mg of this is roughly equivalent to 7.5 mg haloperidol in reducing agitation, measured 2 hours after administration. Peak concentration is reached in < 1 hour. The effects last about a day. 2.1 ml of sterile water from a vial or ampoule is injected into a freeze-dried vial containing 11 mg Zyprexa IM. The vial is rotated to dissolve and mix the contents. The required volume is withdrawn to obtain the correct dosage³⁸¹⁸. It should only be given intramuscularly, never IV or SC. It can be given on a maximum of 3 consecutive days. The starting dose is 10 mg (elderly or in people with hepatic or renal impairment = 2.5-5 mg). A second injection of 5-10 mg can be given 2 hours later if necessary. The maximum daily dose is 20 mg (combined oral plus IM). No more than 3 injections should be administered over a 24-hour period. These instructions should be strictly adhered to.

Adverse effects of Zyprexa IM

Somnolence

³⁸¹⁴ It is essential that all known data are released if the frequency of adverse results are to be calculated accurately.(Dyer, 2007)

³⁸¹⁵ E.g. constipation and dry mouth – however, sialorrhoea has also been reported.

³⁸¹⁶ Usually transient and asymptomatic.

³⁸¹⁷ 5, 10, 15 and 20 mg.

³⁸¹⁸ 10 mg = 2 ml, 7.5 mg = 1.5 ml, 5 mg = 1.0 ml.

Dizziness Asthenia Hypotension Postural hypotension Tremor Acute dystonia

No significant changes occur in mean QTc duration. Vital signs must be recorded for 2-4 hours after administration. Eight fatalities were reported as of August 31, 2004 (cardiorespiratory arrest, hypotension, and bradycardia). (Lilly, communication of October 1, 2004)

Zyprexa IM should be avoided in patients with unstable medical disorders. **Co-prescription of parenteral benzodiazepines should be avoided if at all possible** (if they are essential they should be given at least one hour after Zyprexa IM).

Olanzapine is 'contraindicated' in elderly patients with dementia-related psychosis and/or behavioural disturbance because of evidence for an association with an increased mortality rate and a greater likelihood of stroke. (Irish Medicines Board, 2004) This is discussed further above.

A true depot preparation of olanzapine, olanzapine palmoate suspension (Zypadhera³⁸¹⁹) (Jones, 2001) and is available. It is given every 2-4 weeks. A rough approximation of dose is got from dividing the dose³⁸²⁰ of injection by the number of days between injections which gives the oral dose/day in mgs. Injection is by deep gluteal injection, making sure a blood vessel has not been entered. Peak plasma levels are reached in 3 days. Weight increase is similar to oral olanzapine. About 1.4% of patients developed a 'post-injection syndrome' (variable in severity, manifestations, and time to occurrence) due to an excessive concentration of olanzapine in blood: sedation, delirium, EPS, dizziness, dysarthria, aggressiveness, raised blood pressure, and seizures. All patients recovered and 70% continued to get the injection. The fact that it may not arise until after a number of injections are administered suggests that faulty injection technique must play some part in its aetiology. (Kane ea, 2010) Treatment is symptomatic. Benzodiazepines may compound sedation when given, for example, for agitation. The patient should not drive or operate machinery on the day of the injection and should be observed for 3 hours after receiving the depot.

Quetiapine fumarate³⁸²¹ (Seroquel) has a greater affinity for 5-HT₂ than D₂ receptors. Both clozapine and quetiapine are loosely bound to the D₂ receptor (compared with typical drugs like haloperidol) and are rapidly displaced by endogenous DA. It causes EPS at the placebo level and does not cause any 'sustained' hyperprolactinaemia (but see Chaudhry ea, 2008) or significant haematological problems. The half-life is 7 hours and 83% is bound to plasma protein. The starting dose is 50 mg/day, half that in the elderly. Seroquel is given twice daily. The optimum dose is probably > 250 mg/day. The starting dose is 50 mg/day and the maximum dose is 800 mg/day³⁸²². *Seroquel XR* (prolonged release: Kahn ea, 2007) is given once daily with 300 mg on day one and 600 mg on day two. The dose range is 400-800 mg/day. However, there may be little difference in outcome 300-400 mg/day and 750-800 mg/day in terms of response rate, change in positive symptoms, and discontinuation due to ineffectiveness or adverse effects. (Painuly, 2010)

³⁸¹⁹ ZypAdhera ®.

³⁸²⁰ Doses in mgs: oral olanzapine 10, 15, and 20/day = ZypAdhera starting dose 210/2 weeks (or 405/4 weeks), 300/2 weeks, and 300/2 weeks respectively = maintenance dose after 2 months of ZypAdhera treatment 150/2 weeks (or 300/4 weeks), 210/2 weeks (or 405/4 weeks), and 300/2 weeks respectively; depending on clinical situation dose may be adjusted within range 150-300/2 weeks or 300-405/4 weeks.

³⁸²¹ A dibenzothiazepine and a derivative of clozapine.

³⁸²² There is a 300 mg tablet.

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Caution is required in the presence of hepatic impairment³⁸²³, cardiovascular disease, hypotensive states, a history of seizures, drugs prolonging the QTc interval, and co-administration of hepatic enzyme inducers or inhibitors. Smoking does not affect quetiapine levels.

Side effects

Somnolence
Dizziness
Postural hypotension
Tachycardia
Syncope
Dry mouth
Indigestion
Constipation
Weight gain³⁸²⁴
Asthenia
Rhinitis
Seizures (uncommon)
NMS (rare)
Transient leucopaenia and eosinophilia
Increased transaminases and gamma-GT levels (asymptomatic and transient)

The possibility of changes in the lens of the eye occurring with longterm use has been raised but there is little evidence to support this.³⁸²⁵ Quetiapine may be useful in Parkinson's disease with psychosis and in Lewy body dementia,(Goldstein, 2000; Hellewell, 2002) but Ballard ea (2005) found that neither quetiapine or rivastigmine were effective in treating agitation in Alzheimer patients³⁸²⁶ and, relative to placebo, quetiapine was associated with significantly greater cognitive decline.

Sertindole (Serdolect)

This atypical drug was withdrawn in 1998 due to QT prolongation.(O'Shea, 1998) It became available again in 2007 as a once-daily treatment for schizophrenia intolerant to at least one other antipsychotic drug³⁸²⁷. It is said to be limbic selective and to selectively inhibit mesolimbic DA neurones and to have balanced inhibitory actions on central D2, 5-HT2 and alpha1 adrenergic receptors. It may be particularly useful for negative (as well as positive) symptoms.(Azorin ea, 2006) Contraindications include hypokalaemia, hypomagnesaemia, history of significant cardiovascular disease, CCF, cardiac hypertrophy/arrhythmia/rate less than 50/minute, personal/family history of congenital long QT syndrome, QTc over 450 msec in males or 470 msec in females, severe liver impairment, pregnancy, and lactation. Placebo level EPS is claimed. Weight gain over 12 months is about 3 Kg. Sedation is not a problem.

Some adverse effects of sertindole

Nasal inflammation/congestion
Reduced volume of ejaculate
Dizziness, postural hypotension
Peripheral oedema
Dyspnoea
Paraesthesiae

³⁸²³ Metabolised by P450 3A4.

³⁸²⁴ With risk of diabetes.(Sernyak ea, 2002)

³⁸²⁵ Some countries requiring six-monthly slit-lamp examinations.(Gunasekara & Spencer, 1998)

³⁸²⁶ Not surprising for rivastigmine since it itself can cause agitation.

³⁸²⁷ Start with 4 mg once daily increasing every 4-5 days. Dose range = 12-20 mg (max. 24 mg). Go slower in elderly and keep upper dose lower.

Prolonged QTc (be careful not to combine with drugs that do same)
Urine positive for red and white cells

Amisulpride (Solian), a substituted benzamide, is highly selective for D2 and D3 receptors³⁸²⁸ and has a higher affinity for limbic than striatal DA sites. Protein binding is low at 16% and drug interactions are unlikely. It is claimed that low doses (50-300 mg/day), which may be selective for presynaptic DA autoreceptors, will alleviate negative symptoms of schizophrenia.³⁸²⁹ (Leucht & Peretti, 2002) Higher doses, like standard antipsychotic drugs, also block postsynaptic DA receptors (400-1200 mg/day in divided doses, max 1,200 mg/day). Some workers wonder if amisulpride is more suited to the treatment of mild to moderate cases of schizophrenia than for severe cases, although others report it to be as effective as olanzapine for acute psychotic exacerbations of schizophrenia, and with significantly less effects on body weight. (Martin ea, 2002; Mortimer ea, 2004) There is a low propensity to induce EPS, (Leucht ea, 2002) at least at modest dosage.

Side effects

Insomnia, anxiety, agitation, somnolence
Gastrointestinal upset, weight increase (less than with risperidone)
EPS including TD
Hyperprolactinaemia with galactorrhoea³⁸³⁰
Hypotension, bradycardia
Rare: allergies, seizures, and NMS
Elderly: hypotension and sedation

The dose should be halved if the creatinine clearance³⁸³¹ is 30-60 ml/min and reduced to a third if it is less than this. Ordinary doses are recommended in the presence of hepatic insufficiency.

Ziprasidone³⁸³² (Geodon) has a high affinity (antagonist) for D2 receptors and an even higher affinity for 5-HT_{2A} receptors. Also interacts with 5-HT_{2C}, 5-HT_{1D} and 5-HT_{1A} receptors³⁸³³. There is moderate affinity for neuronal 5-HT and noradrenaline transporters and for H₁ and α -1 receptors. Ziprasidone inhibits neuronal reuptake of noradrenaline and serotonin. It has negligible affinity for M₁ receptors. Higher doses (e.g. 160 mg/day), as with olanzapine and risperidone, can cause EPS. Somnolence is a relatively common adverse effect. It can prolong the QT interval.³⁸³⁴ If the prolactin level rises it tends to normalise over time. Upper respiratory symptoms and rhinitis may occur.

Contraindications

Hypersensitivity³⁸³⁵

³⁸²⁸ More selective than sulpiride.

³⁸²⁹ But Speller ea(1997) found that low-dose amisulpride was similar to low-dose haloperidol in terms of negative symptom alleviation.

³⁸³⁰ Mortimer (2002) states that amisulpride has little effect on endocrine function.

³⁸³¹ 24-hour collection of urine and a serum creatinine level are required. **Creatinine clearance** (a GFR surrogate) = $U \times V/P$ = urine creatinine concentration (U) x rate of urine flow in ml/min (V) ÷ plasma creatinine concentration (P). Normal = 90-140 ml/min (males) and 80-125 ml/min (females). Creatine clearance is an assessment of glomerular filtration rate. The Cockcroft-Gault formula states that creatine clearance = $(140 - \text{age}) \times \text{weight in kg} \times 1.23$ (or 0.85 for females) and divide your answer by creatinine in $\mu\text{mol/L}$.

³⁸³² Development of ziprasidone was slowed by prolongation of the QT interval (risk of tachyarrhythmias) but it became available in the US in 2001 and in Ireland in the following year. Oral (40 mg BID with food, max 80 mg BID, and suggested maintenance at perhaps 20 mg BID; reduce dose for hepatic, but not renal, insufficiency) and IM (as mesylate; to control agitated schizophrenic patient; 10-40 mg/day; can give 10 mg every 2 hours; some cases need 20 mg to start; avoid in elderly because of limited experience; lasts three days) forms are available.

³⁸³³ Affinity at least as strong as for D₂ receptor.

³⁸³⁴ Leucht and Peretti (2002) suggest that olanzapine and haloperidol have little effect on the QTc, quetiapine a little more, the risperidone, followed by ziprasidone, with the greatest effect from thioridazine.

³⁸³⁵ As are all drugs.

Known QT prolongation
 Congenital QT syndrome
 Recent MI
 Uncompensated heart failure
 Arrhythmias
 Treatment with certain drugs³⁸³⁶

Schatzberg ea (2005, p. 197) do not routinely do follow-up ECGs on their ziprasidone-treated patients; however, they suggest a baseline and repeat ECG in people with a known history of arrhythmias. Breier ea (2005) found that olanzapine was superior to ziprasidone in terms of reducing psychopathology in schizophrenia, but that ziprasidone caused fewer problems with weight and lipids.³⁸³⁷

Zotepine³⁸³⁸ (e.g. Zoleptil) is structurally related to clozapine. It strongly inhibits noradrenaline reuptake and causes fewer EPS than haloperidol.

Adverse effects

Sedation
 Weight gain
 Increase in liver enzymes (transient)
 Uricosuric activity
 Seizures

Aripiprazole³⁸³⁹ (Abilify): This new antipsychotic quinolinone/dihydrocarbostyryl appears to show high affinity partial agonism at presynaptic D2 receptors but antagonism at postsynaptic D2 receptors³⁸⁴⁰. It is said to be a dopamine system stabiliser (DSS) that strikes a balance between too much and too little DA: its partial agonist action in the brain causes activation where dopaminergic tone is low and inhibition where it is too high. PET studies suggest that 60-80% striatal D2 receptor occupancy accounts for antipsychotic activity among DA receptor antagonists, the incidence of EPS increasing as occupancy surpasses 80%. Aripiprazole occupies up to 95% of striatal D2 receptors, but EPS levels are no higher than with placebo, probably a result of weak partial agonism at D2-like DA receptors.(Gründer ea, 2003) This novel partial dopamine agonist action augments the 5-HT1A and 5-HT2 effects of aripiprazole³⁸⁴¹. It is said to reduce negative and cognitive symptoms when given once daily³⁸⁴². Motor side effects are said to be absent. Hyperprolactinaemia is less pronounced than for risperidone.(El-Sayeh ea, 2006) In fact, adding aripiprazole to a haloperidol regimen may normalise prolactin levels and lead to a return of menstruation.(Shim ea, 2007) There is little effect on the QTc.(Potkin ea, 2003; El-Sayeh ea, 2006)

Side effects

Headache

³⁸³⁶ E.g. class IA and III antiarrhythmics, thioridazine, pimozide, cisapride, etc.

³⁸³⁷ According to Simpson ea (2004) ziprasidone may even lead to weight loss and a decrease in triglycerides. In one meta-analysis (Allison ea, 1999) the following weight gain in pounds was put on over 10 weeks with clozapine or olanzapine – 10, risperidone or quetiapine – 5, and ziprasidone – 1.

³⁸³⁸ Zotepine is available in a number of countries. Daily doses are 50-75 mg (starting), 150-300 mg (maintenance), and 300 mg (maximum).

³⁸³⁹ A partial DA and 5-HT agonist. Tablets: 5, 10, 15, 20 and 30 mgs. Orodispersible tablets come as 10 and 15 mgs. Dehydro-aripiprazole, its major metabolite, has similar D2 affinities as has the parent drug and represents 40% of the parent drug exposure in plasma. Bifeprunox (rejected by FDA in 2007) has similar actions to aripiprazole on DA receptors.

³⁸⁴⁰ Aripiprazole has in fact a high affinity for D2/D3 receptors and dissociated very slowly from these receptors leaving them almost saturated for up to a week following the last dose.(Gründer ea, 2008)

³⁸⁴¹ Suggesting a possible tendency to cause akathisia.

³⁸⁴² Start at 15 mg/day, can then increase to a maximum of 30 mg/day after 2 weeks if necessary. Orodispersible tablets, 10 mg and 15 mg available.

Agitation ³⁸⁴³ Dizziness Somnolence/insomnia Nervousness

Only a small percentage of treated cases put on significant weight. The evidence suggests that aripiprazole has no clinically relevant effect on total cholesterol, triglycerides, HDL and LDL. Plasma levels are increased by ketaconazole (inhibits CYP 3A4), quinidine (inhibits CYP 2D6), and carbamazepine (induces CYP 3A4). Orthostatic hypotension may occur due to alpha-1 antagonism. Use in pregnancy depends on the results of a risk-benefit analysis. Because of lack of data, women taking this drug should not breast feed. It is **not** approved for the treatment of dementia-related psychosis and/or behavioural disturbances because of the danger of cerebrovascular adverse events.

An injectable form of aripiprazole will be available in Ireland soon. (Andrezina et al, 2006)

Iloperidone³⁸⁴⁴ (Zomaril): This new atypical agent, which has yet to be launched (including a depot preparation), is a benzisoxazole derivative and therefore related to risperidone. Iloperidone is described as a broad spectrum DA/5-HT/noradrenaline receptor antagonist with low EPS/weight gain/sedation potential and no detected increase in prolactin. There may be a small dose-dependent effect on QTc.

Sudden death

Postmortem examination is usually negative. Reilly et al (2000) found abnormal QT³⁸⁴⁵ dispersion (and T wave abnormalities) to relate more to lithium therapy than to antipsychotic drugs, whereas antipsychotics, especially thioridazine and droperidol, were associated more with QTc prolongation! Thioridazine more than other antipsychotic drugs, and low potency (like thioridazine) more than high potency (such as haloperidol) have been associated with reports of sudden, unexplained death. (e.g. Mehtonen et al, 1991; Reilly et al, 2002) Reported incidence-rate ratios for sudden cardiac death among users of high-dose antipsychotics (compared to non-users) have varied from 1.72 (haloperidol) to 5.05 (for thioridazine). (Schneeweiss & Avorn, 2009) Drugs such as thioridazine and pimozide (acts as a calcium channel blocker) should be avoided in those patients with a prolonged QT interval or a history of cardiac arrhythmia. In doses > 10 mg/day pimozide causes marked prolongation of the QT interval, and in doses > 20 mg/day it is associated with an increased risk of developing seizures. Glassman and Bigger (2001) reviewed the evidence for sudden death and *torsade de pointes* and found documented reports incriminating pimozide, sertindole, droperidol and haloperidol, with the highest risk associated with thioridazine. There was no evidence implicating risperidone, olanzapine, or quetiapine. Ziprasidone does prolong the QT interval but there was no documented evidence of sudden death or *torsade de pointes* to date.

Dangers of high doses of antipsychotic drugs

Sudden death (hypotension due to peripheral noradrenergic receptor antagonism, and cardiac arrhythmias due to actions at sodium and calcium channels)

Severe EPS (esp. Parkinsonism and akathisia)

³⁸⁴³ Agitation was the commonest reason for discontinuing aripiprazole in a retrospective study of 85 patients. (Shajahan, 2008)

³⁸⁴⁴ According to Miyamoto et al, (2002, p. 778) and compared with clozapine, iloperidone has relatively high affinity for D₁, 5-HT_{2C}, 5-HT₆, 5-HT₇, α₂, and H₁ receptors, and relatively low affinity for D₂, D₃, D₄, 5-HT_{1A}, 5-HT_{2A}, and α₁ receptors.

³⁸⁴⁵ The QT interval is measured from the beginning of the QRS complex to the point where the T wave meets the isoelectric line, the normal being < 420 msec, and > 500 msec increasing the chances of developing torsades de pointes. The QTc is the QT interval (time taken for cardiac electrical system to repolarise) corrected for heart rate. Opinion varies as to which is the most relevant measurement: the QTc prolongation or QTc dispersion, the latter representing the difference between the longest and the shortest QTc interval on the 12-lead ECG.

NMS (possibly related more to rate of dose escalation rather than dose size *per se*)
 Paradoxical deterioration in behaviour
Confusion (high doses of drugs with atropinic effects, e.g. thioridazine)

Regular ECGs have been recommended for patients on high doses of antipsychotic drugs. This may be more readily achievable in some centres than in others.

Schizophrenic patients on antipsychotic drugs who undertake exercise find it harder to lose body heat than do controls, and this is not explicable on the basis of a difficulty with sweating.

There is some evidence that blood levels of haloperidol between 5-30 ng/ml may be therapeutic but that higher levels may be associated with a poorer clinical response. It is important to remember that sudden death in psychiatric patients may be nothing to do with treatment. (Janicak *et al*, 1997; Hennessy *et al*, 2002)

Ray *et al* (2009) looked at risk of sudden death in current Medicaid users of antipsychotic drugs in Tennessee and found that both typical and atypical drugs had a similar dose-related increased risk for this outcome. Adjusted incidence-rate ratios for typical and atypical drugs were 1.99 and 2.26 respectively.

Sudden death in psychiatric patients

Suicide
 Natural causes (e.g. cardiovascular disease)
 Accidents
 Treatment, especially higher doses

Lifestyle factors are important here. (Ruschena *et al*, 1998; Albert *et al*, 2000) Special consideration should be given to patients with known cardiovascular disease. (Ray *et al*, 2001) Some practitioners were sceptical about the decision of the British Committee on the Safety of Medicines in 2000 to restrict the use of thioridazine believing it safer than aspirin, too cheap to be profitable, and only rarely toxic; they also pointed to the not inconsiderable distress caused to patients who have had to stop taking it after many years. (e.g. Bisset, 2002) Others pointed to the need for caution in reducing or withdrawing thioridazine in special populations, e.g. adverse effects such as re-emergence of psychosis and behavioural problems in the intellectually disabled. (Matthews & Weston, 2003) In fact, the main problem with thioridazine was probably excessive dosage, i.e. 600 mg or more per day. (Hennessy *et al*, 2002)

Tetrabenazine (Nitoman)

This drug is mentioned here for convenience. Tetrabenazine is used to treat abnormal movement disorders like Huntington's disease and TD. It depletes neuronal stores of biogenic amines, including DA. Its actions resemble but are less pronounced than those of reserpine. The starting dose is 25 mg/day, increasing to 25 mg tid, the maximum dose being 200 mg/day. It can cause drowsiness, indigestion, hypotension, and Parkinsonism at high doses. If the patient becomes depressed a MARI can be added. MAOIs should be avoided because a confusional state may ensue.

Some anticholinergic-antiparkinsonian drugs

This section deals briefly with aspects of these drugs of special relevance to psychiatry. (O'Shea, 1998) It is not always possible to avoid giving anticholinergic drugs, e.g. a dystonic reaction could be dangerous in a patient in spinal traction. Interestingly, one Missouri-based study found poor compliance with these drugs! (Goad & Ezell, 1990) The available anticholinergic drugs³⁸⁴⁶ are biperiden (Akineton and Akineton Retard, PO)

³⁸⁴⁶ Orphenadrine, which could cause fits and cardiac arrhythmias, was removed from the market. (Buckley & McManus, 1998) Benzhexol (trihexyphenidyl) disappeared from *MIMS Ireland* in 2002 and benztropine (benzatropine) in 2003.

and procyclidine (Kemadrin, PO or IV; the initial recommended IV dose for Kemadrin [10 mg/2 ml] is 2.5 mg).

Side effects of anticholinergic drugs

Blurred vision
 Constipation
 Dry mouth (oral hygiene is essential)
 Reduced sweating (hot/dry skin, risk of heat stroke)
 Delayed or retrograde ejaculation
 Memory problems
 Delirium
 Mydriasis
 Exacerbation of asthma or narrow-angle glaucoma
 Pyrexia
 Photophobia
 Sinus tachycardia
 Urinary retention
 Delayed gastric emptying³⁸⁴⁷

Anticholinergic drugs do have street value as drugs of abuse because of their euphoriant effect. They can be lethal in overdose and can impair learning in young people. (Owens, 2000)

Diphenhydramine (Benadryl; 25-50 mg thrice daily) an H1-blocker, has also been used as a treatment for drug-induced Parkinsonism. It is not a first line treatment. One advantage may be its relative lack of anticholinergic effects (less chance of delirium).

Amantadine³⁸⁴⁸ (Symmetrel - removed from Irish market in 2008.), 100 mg bid to start, potentiates DA release in the basal ganglia and potentiates amphetamine.

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³⁸⁴⁷ Reduced absorption of drugs like L-DOPA and antipsychotic drugs because of gut motility changes and possibly because of increased hepatic metabolism of antipsychotic drugs – therefore anticholinergic drugs reduce plasma antipsychotic drug levels and antipsychotic action is diminished.

³⁸⁴⁸ The adamantane amantadine, a synthetic symmetrical amine and relation of memantine, is active against influenza A but not B. **Side effects of amantadine:** nausea (gastric irritation), dizziness (orthostatic hypotension), insomnia, poor concentration (although memory, especially visual memory, may be less affected than with anticholinergic drugs – may be suitable for elderly patients), irritability, depression, anxiety, ataxia, seizures, ankle oedema, livedo reticularis, visual hallucinations (rare). Owens (2000) is sceptical about the longevity of action of amantadine and suggests that it can cause dyskinesia in the longterm. Overdose can lead to toxic psychosis and cardiopulmonary arrest.

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Tranquillising and Beta-blocking Drugs, and Emergencies

Brian O'Shea

'And you will give yourself peace if you perform each act as if it were your last'. Marcus Aurelius (121-80).

Tranquillisers

Benzodiazepines (BZDs)

It is interesting to note, as pointed out by Ling ea (2003, p. 907), that people do not usually find the subjective effects of sedative-hypnotic drugs to have appeal, unless they are 'predisposed to addiction'. Most BZDs are variations on the basic 1,4-benzodiazepine structure, a 7-membered ring of carbon and nitrogen atoms. These drugs bind to postsynaptic sites at GABAergic synapses. (see box) The latter are especially plentiful in the limbic system, cerebral cortex, cerebellum and spinal cord. BZDs potentiate GABA's inhibitory effect by increasing neuronal permeability to chloride ions, thus making the cell more difficult to excite. Chlordiazepoxide (Librium) and diazepam (Valium – a 2-ketobenzodiazepine) were the first members of this class to be introduced.³⁸⁴⁹ They are very effective, probably as much as were the barbiturates and the propranolols (e.g. meprobamate). Many experts (e.g. Williams and McBride, 1998) counsel practitioners against withholding BZDs from patients with psychiatric illness or withdrawing them from non-problematic longterm users³⁸⁵⁰. Their main indication is for severe anxiety states regardless of aetiology. Diazepam is one of the most widely used, and probably overused, drugs on this planet³⁸⁵¹. There may be a too ready tendency to commence patients on BZDs in general and psychiatric hospitals and units, and such prescriptions may not be reviewed and reasons for prescribing them may not be recorded³⁸⁵² (e.g. Hallahan ea, 2008; Finnerty, 2009) and many such patients remain on these drugs after discharge. (Surendrakumar ea, 1992; Anonymous, 1992) They are relatively safe in overdose. Tolerance to the sedative effects of BZDs often develops but this is disputed for the anxiolytic effects. (e.g. Lader, 2000)

Benzodiazepines

(a) Receptors and tolerance

BZDs, barbiturates and barbiturate-like substances all have their primary effects on the GABA_A receptor complex, which contains a chloride ion channel, a binding site for GABA, and a BZD binding site (alpha-1 to -5 subunits). There is an influx of chloride ions when GABA binds to its receptor. BZDs, barbiturates and barbiturate-like substances increase the affinity of the receptor for GABA, the result being hyperpolarisation (i.e. inhibitory). During longterm BZD intake GABA causes less chloride influx (perhaps the basis of tolerance), i.e. the receptor is down-regulated.)

³⁸⁴⁹ Their active metabolites are desmethyldiazepam (half-life = 30-200 hours) and desmethylchlordiazepoxide (half-life = 28-100 hours) respectively.

³⁸⁵⁰ The short-acting, high-potency BZDs like alprazolam often need a very gradual taper, even stretching to months (e.g. in patients taking alprazolam for more than 2-3 months the dose may be reduced by about 10%/week – if the patient was on 4 mg/day reduce dose by 0.5 mg/week over a period of 8 weeks). Alternatively, alprazolam can be switched clonazepam which may then be tapered over weeks (0.5 mg clonazepam = 1 mg alprazolam).

³⁸⁵¹ Diazepam was probably the subject of the Rolling Stones' 'Mother's Little Helper'.

³⁸⁵² Similar considerations apply to non-BZD hypnotics. (Finnerty, 2009)

BZDs also act at adenosine receptors and at mitochondrial outer membrane. In the later case they may be involved in cholesterol transportation into the mitochondrium and the genesis of neurosteroids.

(b) Classification of benzodiazepines (according to substitution on diazepine ring)

2-keto – chlordiazepoxide, diazepam, flurazepam, chlorazepate, prazepam, halezepam

3-hydroxy – oxazepam, lorazepam, temazepam

Triazolo – alprazolam, triazolam, estazolam

Imidazo – midazolam

2-thione - quazepam

BZDs seem to affect the limbic system (the centre of emotion) by increasing the effects of GABA, the chief inhibitory neurotransmitter in the brain. They have more effect on the reticular and limbic systems and less effect on the cortex than does the barbiturates. In 1977, specific high-affinity binding sites for BZDs were reported in the brain. Such sites are believed to be the primary site of action of BZDs and are found on the same protein as GABA receptors. The search for endogenous ligands³⁸⁵³ is still ongoing. Many chemicals from different classes act on the receptors. The receptor can increase or decrease anxiety levels; i.e. it modulates anxiety levels. Agonists or inverse agonists, decreasing and increasing anxiety respectively, act on this receptor. The elimination half-life of diazepam increases from 20 hours in a young adult to 90 hours at 80 years of age. BZDs, being weakly basic, are well absorbed from the duodenum and they undergo first-pass metabolism. BZDs are firstly metabolised by N-dealkylation or aliphatic hydroxylation. This is followed by conjugation via glucuronyl transferases to water-soluble glucuronides that can be excreted in the urine. Omeprazole delays the elimination of diazepam, phenytoin and warfarin.

BZDs are highly lipid soluble. They are highly protein-bound in plasma and widely distributed to the tissues. Some metabolites are active, such as those of temazepam, oxazepam (less sedative in overdose than temazepam), diazepam and chlordiazepoxide. BZDs cause minimal induction of hepatic microsomal enzymes, which means much less drug interactions than was the case with barbiturates. The rate of metabolism and the nature of metabolites determine duration of action. Heavy smoking may reduce the efficacy of BZDs. BZDs rapidly cross the blood-brain barrier.

There is little to choose between members of the BZD group.³⁸⁵⁴ Diazepam has muscle relaxant and anticonvulsant effects. All 1,4 BZDs are sedative, anticonvulsant and muscle relaxing. Some of the newer 1,5 BZDs, like clobazam (Frisium), are less sedative but still have anxiolytic and anticonvulsant properties. BZD-induced enhancement of GABA function reduced excitability of glutamatergic neurotransmission, accounting for the anticonvulsant action. Clorazepate³⁸⁵⁵ (Tranxene) is a prodrug for N-desmethyldiazepam (nordiazepam), a slowly eliminated metabolite.

A hypnotic is simply a tranquilliser taken whilst going to bed. Flurazepam (marketed as a hypnotic) may be given by day and diazepam (sold as a tranquilliser) by night.

Half-lives (hours) of some BZDs

Diazepam, 20-90

Chlordiazepoxide, 5-30

Nitrazepam, 18-36

Temazepam 4-10

Lorazepam, 5-10

Oxazepam, 5-10

³⁸⁵³ Substances naturally found in the brain, which act in the same way as the exogenous substance under consideration.

³⁸⁵⁴ Examples of BZDs are diazepam (Valium, Diazepam, Atensine), chlordiazepoxide nitrazepam, flurazepam (Dalmane), temazepam (Normison, Tenox, Euhypnos - this and flunitrazepam (Rohypnol; street names include forget-me pill, Mexican Valium, R2, roofies, roofinol, rope, and rophies) have been controlled drugs in Ireland since 1993; addicts had injected liquid capsule contents – intra-arterial temazepam can cause tissue necrosis and rhabdomyolysis), triazolam (banned in UK in 1991 because of concerns over [anterograde] amnesia-induction [of use before minor surgery], rebound anxiety, aggression, excitation, psychosis, and fatality in overdose), lormetazepam, lorazepam, prazepam, medazepam, potassium chlorazepate, alprazolam, and loprazolam.

³⁸⁵⁵ Chlorazepate (Tranxene), withdrawn 2006.

Triazolam, 2-4

Triazolam, midazolam and brotizolam are short-acting BZDs with half-lives of about 6 hours. Lormetazepam, lorazepam and temazepam are medium-acting with half-lives of 6-12 hours. Long-acting BZDs (half-life > 12 hours) include nitrazepam, flurazepam and flunitrazepam.

Benzodiazepines (by half-life)

<i>Long</i>	<i>Intermediate</i>	<i>Short</i>
Chlordiazepoxide	Alprazolam	Brotizolam
Chlorazepate	Bromazepam	Midazolam
Clobazam	Flunitrazepam	Triazolam
Diazepam	Lorazepam	
Flurazepam*	Lormetazepam	
Ketazolam	Nitrazepam	
Medazepam	Oxazepam	
Przepam	Temazepam	

*The long half-lives of flurazepam and quazepam are a result of their metabolite desalkylflurazepam.

Two forms of diazepam are worth noting: Diazemuls (5-10 mgs – 5 mg/ml) which is given IV or by infusion, and Stesolid (5-10 mgs) which is given rectally. Where available, IV or IM midazolam (Hypnovel amps 10 mg/2 ml) is given in preference to diazepam because of faster absorption and less local pain. (see TREC Collaborative Group, 2003) If diazepam is put into a bag for IV infusion it will crystallise in a dextrose solution but dissolve in normal saline; venous thrombosis and phlebitis may occur at the infusion site.

BZD abstinence syndrome

Hyperacusis
Photophobia
Paraesthesiae
Hypersomnia
Hypersensitivity to touch and pain
GIT disturbances
Headaches
Muscle spasms
Seizures
Vertigo
Sleep disturbance

Certain symptoms suggest true withdrawals rather than an exacerbation or return of the original anxiety: nausea, anorexia, objective depression, depersonalisation or derealisation, hyperacuity of sensory perception (smell, sight, taste, and touch), and abnormal perception or sensation of movement. BZD abuse is not associated frequently with escalating doses. Someone can be deemed to be dependent on BZDs while continuing to consume them in therapeutic doses. Significant withdrawal effects may be more common in patients on BZDs for years and in those with a personality disorder, predominantly of the dependent type. Therapeutic withdrawal may need to be extended to several months in such cases. However, abstinence symptoms may occur after as little as a few weeks taking BZDs and in such cases the dose should be reduced by about an eight

every fortnight. Some people are helped to withdraw if started on an antidepressant drug some weeks before commencing withdrawal of the BZD.

Typical BZD abuser (relative to opiate abuser) (O'Connor & Stafford-Johnson, 1990)

Older
 Female³⁸⁵⁶
 Have abused BZDs for many years
 Relatively well educated
 No legal history
 History of being employed or homemaker
 Good support from family and spouse
 Have abused alcohol prior to abusing tranquillisers
Risk factors for BZD dependence (Livingston, 1994)
 Longterm use
 High doses
 High potency (e.g. lorazepam and alprazolam)
 Dependence on alcohol or other substances
 Personality disorder
 Non-prescription BZD use
 Risk factors associated with (Atkinson, 1997)

(a) *The drug*

Longer treatment duration
 Higher dosage
 Shorter half-life
 High milligram potency

(b) *The patient*

Past or concurrent alcohol or sedative drug dependence
 Chronic insomnia (rather than anxiety) as target of drug therapy
 Coexisting chronic painful illness
 Personality disorder
Long-term users of daytime BZDs in a general practice (Salinsky and Doré, 1987)
 Used age and sex matched controls.
 Crown-Crisp index showed revealed a chronic neurotic disposition
 Most were women in late middle age or older
 79% felt that the treatment was helpful
 BZD use seemed to declining rapidly
 Authors felt doctors express concern about overuse/misuse of minor tranquillisers
Long term users of BZDs in USA (Salzman, 1990)
 Older, medically ill patients
 Panic disorder patients
 Chronically dysphoric patients
 Chronic sleep-disordered patients
 Chronically psychotic patients where BZDs were used adjunctively with antipsychotic drugs

A number of authors have suggested that BZD abuse is strongly associated with abuse of other drugs, including alcohol. Intravenous BZD abuse in Britain became a problem from the mid-1980s and the main drugs used were temazepam³⁸⁵⁷, flurazepam, diazepam, triazolam and nitrazepam.

³⁸⁵⁶ Women may be prescribed BZDs more often than are men.(van der Waals ea, 1993)

³⁸⁵⁷ Despite the capsular content being changed from liquid to semisolid gel in 1989. Intra-arterial lorazepam may cause gangrene, muscle necrosis and myoglobinuria.

The risk of a serious road traffic accident is five times greater for BZD users than for non-users.³⁸⁵⁸

Common side effects of BZDs

Taste in mouth

Hangover

Ataxia

Confusion in elderly

Rebound insomnia on withdrawal (withdraw slowly)

Chronic therapeutic dosage with BZDs in elderly may cause

Poor recall

Forgetfulness

Impaired concentration

(Simulating a, usually mild, dementia)

Paradoxical/disinhibitory reactions

Irritability, aggressiveness

Occur in a few patients³⁸⁵⁹

Good practice dictates prescribing on a PRN (*pro re nata*, as required) basis or for a week or two at a time. Seizures may be more likely after withdrawal of short-acting BZDs. They can occur as early as 24 hours after stopping the drug. The prescriber should gradually stop them and consider substituting long-acting BZDs during the withdrawal period.

About two-fifths of regular users of BZDs develop pharmacological dependence and have withdrawal symptoms when the dosage of their drug is reduced or when treatment is stopped. (Tyrer, 1988). Withdrawal symptoms occur within 2-3 days of stopping short-acting BZDs and within 7 days of stopping their longer-acting relatives. They last for one to two weeks. (Owens, 2004, p. 300) Carbamazepine (Tegretol) may reduce the effects of withdrawing benzodiazepines. (O'Shea, 1989) especially if dosage reduction is rapid, although the effect is not marked. Propranolol, a beta-blocking drug, has slight ameliorative effects. A shift from long- to short-acting BZDs may alleviate subsequent abstinence effects. If necessary, BZD dependent patients who are detoxified from these drugs might be helped to stay off them if prescribed trazodone 10 mg tid. (Anseau & De Roeck, 1993) Lader (1994) recommends a 4-week detoxification period (some people need a much slower detoxification). Shapiro et al (1995) suggest shifting to zopiclone. Voshaar et al (2006) found no benefit for psychotherapy in terms of abstinence rates. Frequent, high doses of alprazolam have been used in the management of panic disorder. It must be withdrawn extremely slowly.³⁸⁶⁰ Perhaps its main use should be in the acute detoxification of alcoholics. Its role as an adjunct in the treatment of depression is probably not unlike that of other benzodiazepines. (O'Shea, 1989)

Pregabalin (Lyrica)

This non-BZD relative of GABA is indicated in adults (only) for anxiety disorders, particularly GAD, (Rickels et al, 2005) peripheral neuropathic pain, and as adjunctive therapy for partial seizures, and perhaps fibromyalgia as well. It appears to be effective and safe in elderly GAD patients. (Montgomery et al, 2008) It binds to a subunit of the

³⁸⁵⁸ The risk is increased with age, taking alcohol, dose, and long half-life drugs.

³⁸⁵⁹ According to Paton (2002) those at highest risk are patients with impulse control problems, neurological disorders, intellectual disabilities, and < 18 years or > 65 years of age.

³⁸⁶⁰ The Van der Kroef reaction (Van der Kroef, 1979) is the collective term used to describe a withdrawal syndrome associated with the abrupt discontinuation of triazolam (Halcion). It consists of depersonalisation, derealisation, paranoid ideation, suicidal thoughts, nightmares, and anxiety. It has also been described in association with alprazolam (Xanax) discontinuation. (Browne & Havge, 1986).

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calcium channel³⁸⁶¹ and has other downstream effects. The starting dose is 150mg/day (75 mg bid). The usual dose range is 150-600mg/day³⁸⁶². The medication should be tapered gradually when it is being discontinued. Dosage adjustment is required for renal (and haemodialysis), but not hepatic, impairment. Avoid pregabalin in people with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption and caution should be observed concerning driving/using machinery. Weight gain in diabetics may require regime change. Pregabalin causes excess sedation if combined with oxycodone and may potentiate the effects of alcohol and benzodiazepines.

Pregabalin

Withdrawal symptoms

Insomnia, nervousness, depression

Headache

Nausea, diarrhoea

Flu-like symptoms

Pain

Sweating

Dizziness

Side effects

Somnolence*

Dizziness*

Euphoria, confusion, irritability, feeling drunk, poor attention, impaired memory, fatigue

Ataxia/abnormal coordination, tremor, dysarthria, paraesthesia

Blurred vision, diplopia, vertigo

Decreased libido, erectile dysfunction

Dry mouth, constipation, vomiting, and flatulence

Peripheral oedema

Weight increase

*Most common

It may worsen cognitive and motor effects of oxycodone and increase the effects of alcohol and BZDs. Pregnancy is a contraindication unless a risk-benefit analysis favours its use; women of childbearing years should be protected against pregnancy; and breast-feeding is not recommended.

Flumazenil (Anexate)

Flumazenil, a BZD receptor antagonist and 1,4-imidazobenzodiazepine resembling midazolam, reverses the sedation produced by BZDs (and 'Z' drugs) and may have some role in helping patients withdraw from these drugs. It seems as if BZD dependence is associated with an allosteric change in the benzodiazepine receptor³⁸⁶³. Flumazenil may reset the receptors for normal function. It has minimal effects on the normal CNS and can be given IV, IM or orally. It lasts for 15-140 minutes after a single IV injection (elimination half-life = 50 minutes). When flumazenil is used after brief procedures using BZD premedication or anaesthesia one may need to repeat the injections or to give it as an infusion. This is because most BZDs are longer acting than flumazenil. Flumazenil has an elimination half-life of one hour and the liver mostly inactivates it. Re-sedation may follow 1-2 hours after giving flumazenil. The initial adult dose is 200 micrograms, with

³⁸⁶¹ An auxiliary subunit (alpha2-delta protein) of voltage-gated calcium channels in CNS, causing a potent displacement of [³H]-gabapentin.

³⁸⁶² The dose may be increased from 75 mg bid to 150 mg bid after 3-7 days and then, if required, the dose may be increased after an additional 7 days.

³⁸⁶³ This augments the action of inverse agonists.

further 100 microgram increments at 60-second intervals until sedation is reversed, up to a maximum of 2 mg.

Day anaesthetic cases will still not be able to drive home or to travel unescorted, in case of late-onset re-sedation. In a BZD overdose flumazenil is unlikely to improve the outcome but it may clarify the diagnosis. In cases of *mixed TCA-BZD overdose* flumazenil may cause arrhythmias and seizures, the latter being TCA effects controlled by the BZDs. Flumazenil should not be given to *ventilated patients who have raised intracranial pressure following head injury* as the drug will raise the intracranial pressure even further and reduce cerebral perfusion pressure.

Side effects of flumazenil

Nausea, vomiting
Dizziness, headache
Flushing
Agitation, anxiety, confusion
Seizures (especially in epileptics)
Transient tachycardia and hypertension

The 'Z' drugs (zopiclone, zolpidem, zaleplon)

Conclusions drawn from NICE on these drugs suggest that the methodology of studies carried out were defective for a number of reasons³⁸⁶⁴. No consistent difference was found between these drugs and BZDs for effectiveness or safety, and the Z drugs are several times more costly than BZDs.(Holbrook, 2004) This caveat should be kept in mind when reading about each of these drugs. Ecause there is a risk of inducing dependence, they should be employed cautiously for short-term treatment of insomnia.

Zopiclone³⁸⁶⁵ (Zimovane, Zopitan, Zorclone)

This non-BZD cyclopyrrolone derivative is a mildly sedative drug marketed as a hypnotic. The elimination half-life is only 3-8 hours. Zopiclone facilitates GABA by acting on BZD receptors at a site close to, rather than identical to BZDs, i.e. the omega site. Even though zopiclone is not a BZD, its actions are blocked by flumazenil. The suggested dose is 7.5 mgs nocte (range, 3.75-15 mgs). The tablet can be broken in half (3.75 mg) for elderly patients. The patient may experience a bitter or metallic taste in the mouth. Withdrawal can cause rebound insomnia and also to craving and anxiety.(Jones & Sullivan, 1998) Zopiclone may increase TCA metabolism. Carbamazepine increases plasma zopiclone levels. Care should be taken when driving.(Barbone ea, 1998) According to Shapiro ea,(1995) zopiclone may facilitate withdrawal from BZDs. Bannan ea (2005) highlighted the misuse of patients attending a Dublin methadone maintenance programme, detected by finding its breakdown product³⁸⁶⁶ in urine. Moloney ea (2007) reported two cases of depression whose agitation ceased when zopiclone was stopped.

Zolpidem (Stilnoct, Nytamel, Zolnod)

Zolpidem has a higher affinity for BZ1 than for BZ2 receptors. This hypnotic³⁸⁶⁷ should be avoided in the presence of obstructive sleep apnoea³⁸⁶⁸, myasthenia gravis, severe hepatic insufficiency, acute pulmonary insufficiency, or respiratory depression.

Potential side effects

Malaise
Drowsiness
Dizziness

³⁸⁶⁴ E.g. selective reporting of positive findings, short duration, suboptimal comparators, and use of surrogate markers such as sleep variables.

³⁸⁶⁵ The hypnotic agent eszopiclone (Lunesta in the USA) is an enantiomer of zopiclone.

³⁸⁶⁶ 2-amino-5-chloropyridine.

³⁸⁶⁷ An imidazopyridine; half-life = 2-4 hrs; mainly metabolised by conjugation; no active metabolites; reversed by flumazenil.

³⁸⁶⁸ Although others see it as harmless.(Neylan ea, 2003, p. 978)

Diarrhoea
 Headache
 Memory problems
 Nightmares, somnambulism, night eating disorder
 Nausea, vomiting
 Dysphoria
 Vertigo
 Compulsive behaviours, e.g. repetitive shopping or cleaning (Madden ea, 2009)
 Visual hallucinations, confusion, depression (Wang ea, 2001)
 Falls leading to fractures (Adverse Drug Reactions Advisory Committee, 2002)
 Possible increased daytime anxiety if drug stopped suddenly
 Laboratory animals self-administer zolpidem (possible dependence)

Zolpidem lacks muscle relaxant effects and is said to have minimal effect on sleep architecture (total REM and REM latency usually unmodified). Zolpidem is much less likely to be associated with rebound of REM or insomnia than are the BZDs. It is secreted in breast milk. The dose should be reduced in cases with hepatic or renal impairment. The action of the drug may last longer in the elderly and it may be foreshortened in children. The average dose is 10 mg for adults and 5 mgs for the elderly, taken just before sleep. The combination of zolpidem with an SSRI may potentially cause delirium.(Coleman & Ota, 2004)

Zaleplon (Sonata)

This pyrazolopyrimidine hypnotic³⁸⁶⁹ binds selectively to BZD type I receptors, has an extremely short elimination half-life of about 60 minutes, and is metabolised in the liver. Inactive metabolites are excreted in urine (17%) and faeces (17%). The dose should be halved in the presence of hepatic insufficiency but no dose adjustment is required for renal insufficiency. Sleep architecture is unaffected. It may be useful for jet lag. Contraindications include severe liver insufficiency, hypersensitivity, sleep apnoea, myasthenia gravis, severe respiratory insufficiency, and people less than 18 years of age (for whom data is lacking). Its short half-life makes it useful for sleep onset problems. Food delays the onset of maximum plasma concentration by two hours (normally reached in 1 hour). Cimetidine³⁸⁷⁰, ketoconazole, and erythromycin increase Zaleplon's plasma level. Rifampicin reduces its plasma volume. Carbamazepine and phenobarbitone may also reduce the efficacy of zaleplon. Alcohol should be avoided. Zaleplon appears in breast milk. Patients on zaleplon should be advised that driving skills might be adversely affected (do not use within 5 hours of driving). Rebound insomnia and abstinence symptoms are said to be minimal.

Potential side effects

Somnolence
 Mild headache
 Asthenia
 Dizziness
 Anterograde amnesia
 Unmasking of depression
 Paradoxical reactions

Indiplon

This new pyrazolopyrimidine (like zaleplon but more potent) starts to act in less than 60 minutes and has a half-life of about one-and-a-half hours. It can be used in immediate or extended release forms.

³⁸⁶⁹ 10 mg nocte, except for 5 mg at night in the elderly – can be repeated during the night on waking.

³⁸⁷⁰ By 85%.

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Buspirone (Buspar)

Buspar was withdrawn by Bristol-Myers Squibb in late 2009 'for operational reasons'. Buspirone, an azaspirodecanedione and a 5-HT-1A partial agonist (in brainstem raphe nuclei) and a weak dopamine antagonist, takes 1-2 weeks to produce full therapeutic effect. Buspirone, a failed antipsychotic, is indicated for the short-term (!) management of anxiety. Buspirone is a partial DA agonist.³⁸⁷¹ There may also be some DA antagonism because there have been single cases of acute myoclonus and akathisia, and oral dyskinesia. The starting dose is 5 mgs B.I.D. to T.I.D. This can be increased every 2-3 days. The usual therapeutic dose is 45 mgs/24 hours. It does not prevent BZD withdrawal symptoms³⁸⁷². Some studies have found that patients with experience of BZDs do not respond to buspirone and others have found the opposite.(Hollander & Simeon, 2000, p. 569) 5-HT-1A partial agonists (buspirone, gepirone, and ipsapirone) are ineffective for panic disorder and may make the symptoms worse.(Deakin ea, 2001) Buspirone should not be combined with MAOIs.

Side-effects (usually mild)

Dizziness

Headache

Nervousness

Lightheadedness

Palpitations

Chest pain

Drowsiness

Confusion

Dry mouth

Tiredness

Sweating

Tachycardia

Raised prolactin levels and exacerbation/precipitation of EPS (Owens, 2004, p. 300)

According to Harrison-Read ea, (2004, p. 466) buspirone may have limited application because of delayed action and 'dysphoric' effects. It lacks the hypnotic, anticonvulsant and muscle relaxant properties of the BZDs and there is no cross-tolerance with alcohol and no physical dependence when it is given over the long-term to animals.

Melatonin (Circadin)

This contains prolonged-release melatonin 2mg tablets for 'short-term' (3 weeks) treatment of 'primary' insomnia in people aged at least 55 years or more. It is taken 1-2 hours before retiring and after food. Anonymous (2009) believes that the evidence for efficacy of this product is limited. Caution is advised in the presence of renal insufficiency and it is to be avoided in the presence of pregnancy/lactation, liver impairment, or autoimmune disease. It may impair driving or the handling of machinery. Patients with problems relating to galactose or those taking fluvoxamine should not take this tablet. Adverse effects include headache, sore throat, back pain, and asthenia.

Ramelteon³⁸⁷³

This MT1 and MT2 melatonin receptor selective agonist and hypnotic may lack abuse potential and have safe motor and cognitive profiles. (Johnson ea, 2006) It has been associated with raised prolactinand decreased testosterone levels.

Tasimelteon

³⁸⁷¹ It is possible that 1-(2-primidinyl) piperazine, one of its metabolites, may contribute to its long-term pharmacological effects.

³⁸⁷² Therefore, BZDs should either be withdrawn slowly before contemplating the use of buspirone or they should be tapered slowly after the patient is taking buspirone for, say, a month.

³⁸⁷³ Rozerem in the US.

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This MT1 and MT2 melatonin receptor selective agonist and hypnotic improves sleep latency and maintenance. (Rajaratnam et al, 2009)

Ropinirole (ReQuip)

This is a non-ergoline DA agonist. It may rarely cause sudden onset of sleep during daily activities. Patients should not drive.

Carisoprodol (Soma)

This centrally acting muscle relaxant has become a drug of abuse in the US. It is metabolised to meprobamate. Preparations may contain various analgesics including opioids. It can lead to stimulation or depression of the CNS. Tachycardia, hypotension, agitation, nystagmus, coma, seizures, and death from aspiration have been reported. Poisoning from salicylates or paracetamol (contained in the same preparation) should be considered. Flumazenil should not be used.

Orexin antagonists

Orexins are released during waking hours and orexin antagonists may have some use in treating insomnia.

Kava³⁸⁷⁴ (Piper methysticum³⁸⁷⁵)

Derived from a Polynesian root, its mild anti-anxiety effects may be due to kavapyrones³⁸⁷⁶ that are central muscle relaxants. These chemicals are involved in GABA receptor binding and inhibition of reuptake of N-Ad. Gastrointestinal upset, headache and dizziness are the main side effects. Poisoning may lead to hair loss, breathing and vision problems, yellow skin³⁸⁷⁷, and severe liver damage.³⁸⁷⁸ Parkinsonism may also be a side-effect of kava. (Lees et al, 2009)

Beta-adrenergic receptor-blocking drugs (β -blockers)

The main psychiatric uses of this group of drugs are stage fright, akathisia, and the long term management of violence in patients with brain disease³⁸⁷⁹. Use of high doses in schizophrenia is no longer popular.

Contraindications

Ostructive airways disease

Severe ventricular dysfunction

Relative contraindications³⁸⁸⁰

Diabetes mellitus

Peripheral vascular disease (incl. Raynaud's disease)

Bradycardia

Heart block³⁸⁸¹

Insomnia and vivid dreams may occur during treatment with beta-blockers, especially propranolol (because it is more lipophilic and therefore crosses the blood-brain barrier readily). Initial hopes of using beta-blockers to prevent PTSD proved to be disappointing. There have been reports of propranolol-induced delirium. It is also associated with nightmares, depression and drowsiness. Propranolol uncommonly causes depression, other beta-blockers less so. By way of contrast, atenolol, (e.g. Adalat, Atecor) which is

³⁸⁷⁴ Banned in France and carries a warning from the FDA in the US.

³⁸⁷⁵ 'Intoxicating pepper'.

³⁸⁷⁶ These are related to myristicin found in nutmeg.

³⁸⁷⁷ The skin may be pellagra-like: dry and flaky skin, red eyes, and discoloured hair.

³⁸⁷⁸ There may be an eosinophilia. Liver transplantation has been required in a number of cases.

³⁸⁷⁹ Doses in organic brain disorders might be metoprolol (e.g. Betaloc) 200-300 mg/day or propranolol slowly increased to 1 g/day.

³⁸⁸⁰ Beta-blockers are often used for stable heart failure but may exacerbate acute cardiac failure.

³⁸⁸¹ Some authorities list heart block as a full contraindication.

water-soluble and is largely excreted unchanged by the kidneys, rarely causes central side effects.

Beta-Blockers may cause

Lassitude
 Depression³⁸⁸²
 Poor concentration
 Nightmares and other sleep disturbances
 EEG changes
 Hallucinations and psychosis
 Impaired short-term memory
 Cold hands

Beta-Blocker drug toxicity

Mild – bradycardia
 Severe – coma, hypotension, convulsions +/- delirium, hallucinosis, cardiac arrest
 Management – IV glucagon (or, less reliably, IV atropine)

Beta-blockers affect brain function, though less severely than would low-dose BZD. They seem unlikely to affect driving skills. People doing skilled work involving memory and vigilance or careful thought are most vulnerable. Drugs like cimetidine and the SSRIs decrease metabolism of beta-blockers with the potential for severe bradycardia. Beta-blockers should be withdrawn slowly to avoid cardiac rebound phenomena.

Beta-blocker abstinence syndrome

Arrhythmias
 Exacerbation of angina
 Myocardial infarction

Violence & psychiatric emergencies

'Alcohol, without question, is the greatest contributor to violence.' (Hughes, 2000)

'.....much of the violence in society is related to factors such as economics, drug dealing, and other criminal activities not within the usual realm of psychiatric expertise....' (Tardiff, 2003)

'Environmental precipitants are as important as underlying psychiatric or medical diagnoses when determining a patient's level of dangerousness.' (Sanders, 2004, p. 505)

Dangerousness is hard to predict and attempts are at best 'an inexact science'. (Dolan & Doyle, 2000; RCPsych, 2008) Nevertheless the risk of a patient harming themselves or others should be part of psychiatric assessment. It is not something which should be confined to forensic psychiatric work. Various measures³⁸⁸³ are employed in assessing risk.

³⁸⁸² Debatably so. (Long & Kathol, 1993)

³⁸⁸³ The *Glasgow Risk Screen* (NHS Greater Glasgow, 2005: *Report of the Audit of the Use of the Glasgow Risk Screen.*) is an attempt at transparent, systematic and multidisciplinary clinical risk assessment. It comprises categorical identification of a number of historical, precipitating and protective factors organised under self-harm, violence, neglect and other risks.

The *Historical, Clinical and Risk Management – 20* (HCR-20: Webster ea, 1997) consists of non-weighted items that require clinical judgment in determining level of risk (low, medium, high): historical (past violence, young when first violent, unstable relationships, employment difficulties, drug use problems, major psychiatric disorder (MPD), psychopathy, early maladjustment, personality disorder, prior supervision failure), clinical (poor insight, negative attitudes, active symptoms of MPD, impulsive, non-response to treatment), and risk management (plans not likely to succeed, destabilising forces, low personal supports, non-adherence with remediation attempts, stress). In other words: a composite of 20 risk factors for violence: 10 stable past risk factors, 5 current/changeable clinical items, and 5 situational items.

*Some questions to be asked during risk assessment*³⁸⁸⁴

What is the risk of suicide, self-neglect, and being exploited?

What is the risk of homicide?

Are there vulnerable people at risk, e.g. children, spouse, employer, doctor, etc?

From a medico-legal standpoint ones notes must allow the reader to understand what information was gathered and considered and the reasoning process guiding decision-making.(McNiel ea, 2008)

Murders increased by 22% in England and Wales during World War II (Davies, 2006, p. 382)
 US Supreme Court rejected APA position on difficulties involved in predicting dangerousness in *Barefoot v Estelle* 463 US 880 (1983)
 Patients with Capgras delusions may kill (de Pauw & Szulecka, 1988)
 About 1.6 million people worldwide died as a result of violence in 2000, about half attributable to suicide, almost one in three to homicide, and approximately a fifth to armed conflicts (Ghodse, 2006)
 Past dangerousness is the most important predictor of present dangerousness (Maden ea, 2004)
 Major predictor of aggression after head injury is pre-injury antisocial behaviour
 Drug and alcohol abuse³⁸⁸⁵, a frightened psychotic, and mania or antisocial personality disorder, are other common associations (Putkonen ea, 2003; Monshouwer ea, 2006)
 Commonest victims of violence are young men who often go out in the evenings
 If domestic violence is included, then women may be the commonest victims
 Incidence of battered wives is unknown but over 90% of victims of domestic violence are women.
 Reported cases of domestic violence in UK: lifetime prevalence is 25% of women and annual prevalence is one in nine women (Mezey & Robbins, 2000)
 Most women will either not disclose source of their injuries to doctor, or will only hint at it
 Not all studies agree that domestic violence is one way, e.g. according to a British Home Office survey,(Home Office, 1998) 4.2% of women and the same percentage of men reported being assaulted physically by a current or former partner in the past year
 Mentally ill are more likely to be violent toward persons who have close personal contact with them than to strangers (Das ea, 2002)
 Psychotic subjects are often the victims of violence, especially in the presence of severe mental symptoms, homelessness, substance misuse, previous violent behaviour, or comorbid personality disorder (Walsh ea, 2003)
 Berzins ea (2003) found harassment of mentally ill living in the community (41%) to be twice as common as harassment of general population (15%)
 Pressure into unwanted, and often unprotected, sex is not uncommon in histories of psychiatric patients (Wainberg ea, 2003, p. 117)
 Inner city people with severe mental illness requiring admission often have recent histories of aggressive behaviour and of being victims of assault, and men (47%) more than women (17%) will have had at least one conviction for violent crime (Hodgins ea, 2007)
 Either sex with severe mental illness who develop conduct disorder by mid-adolescence are at risk of being aggressive and violent.(Hodgins ea, 2008)
 Actuarial instruments³⁸⁸⁶ can be used to predict violent recidivism in mentally disordered offenders, although they may over-predict reconvictions.(Snowden ea, 2007)
 Schizophrenic patients feel safer outside cities and their being attacked is associated with their abusing alcohol and drugs and having been arrested in the past.(Schomerus ea, 2008)
 1.43 million deaths occur worldwide annually from violent acts, mostly individual acts.(Siever, 2008)
 10-year-old who eat confectionery every day are at increased risk for being convicted for violence at age 34 years, probably because sweets were used to control their behaviours, thus preventing their learning to defer gratification.(Moore ea, 2009)
 Excessive partner alcohol abuse and violence in India increased risk for common mental disorders 2 to 3 times; to some extent women's condoning of violence has a part to play here and should be addressed.(Nayak ea, 2010)
 Inter-partner violence is more common in those with a history of child sexual abuse.(Friesen ea, 2010)

³⁸⁸⁴ See, e.g. Royal College of Physicians and RCPsych (2003) and RCPsych.(2008) The latter (RCPsych, 2008) points out that accurate prediction is impossible in individuals due to complexity of underlying factors and that assessment should relate to the current situation rather than trying to predict a particular event.

³⁸⁸⁵ Arendt ea (2007) suggest that some people may use cannabis to help curb aggression.

³⁸⁸⁶ E.g. *Violence Risk Appraisal Guide* and *Offender Group Reconviction Scale*. The *Buss-Durkee Hostility Inventory* (Buss & Durkee, 1957) is a 75-item self-report questionnaire that measures aspects of hostility and aggression. There are eight subscales: assault, indirect hostility, verbal hostility, irritability, negativism, resentment, suspicion, and guilt. The *State-Trait Anger Expression Inventory* (Spielberger, 1991) is a 44-item scale.

In the Werner ea (1983) study, psychologists and psychiatrists agreed which patients would be violent and what the critical predictor variables were, but empirical correlations of violence with these variables indicated that the judges' predictions were rarely accurate. Sensible precautions are necessary to minimise violence against staff, particularly in the community.

Rampton special hospital, England (Larkin ea, 1988)
Violent incidents more common than in general psychiatric hospitals
A small number of patients accounted for most of incidents
Female patients accounted for 75% of incidents but only 25% of hospital population
Nurses Assaulted three times more often than were patients
St Brendan's Psychiatric Hospital, Dublin (O'Shea, 1988)
Male psychiatrists attacked more frequently than female colleagues
Novice psychiatrists at higher risk from patient-perpetrated violence than are experienced colleagues
Acute psychiatric wards, Exeter (Wildgoose ea, 2003)
Most staff experienced at least one incident of actual/threatened violence within previous year
This was reflected in scores on measures of psychological distress
Factors that may reduce likelihood of violence on a psychiatric ward (Davison, 2005)
Adequate staffing levels
Predictability of ward routine
Pleasant environment
No overcrowding
Wide range of meaningful things to do
Sufficient privacy and dignity
Adequate observation
English national psychiatric ward audit (Chaplin ea, 2006)
Questionnaire and environmental inspection
78% of nurses reported experience of violence
37% of service users reported experience of violence
Concerns over staffing levels, training, provision of activities, ward design/ambience
National Epidemiologic Survey on Alcohol and Related Conditions in US (Elbogen & Johnson, 2009)
Incidence of violence is higher for mentally ill *but only significantly so if there is drug abuse/dependence*
Severe mental illness on its own does not predict future violence
Future violence predictors: past violence, juvenile detention, physical abuse, parental arrest record; clinical (drug abuse, perceived threats); age, sex, income; recent divorce, unemployment, and victimisation
Anonymous questionnaire study of psychiatrists working in Republic of Ireland (Kavanagh & Watters, 2010)
Potential number of respondents = 330; response rate only 48.2%
Being longer in psychiatry in not reduce the rate of being assaulted – however, respondents were only asked if they at one of 3 stated grades at the time of the assault and most of one's career would presumably be as a senior practitioner (O'Shea [1988] broke down level of experience into 5-year chunks and found that lack of experience predicted being a victim)
Standard safety equipment is far from ubiquitous and many psychiatrists had not been trained in safety techniques

The first victim support scheme in Britain was established in Bristol in 1974, and by December 1987 there were 350 schemes. A central advisory body, the National Association of Victim Support Schemes, was formed in 1979. These schemes supply 'everything from emotional support to information about compensation'. A British government enquiry, launched after eight people had been killed in the NHS since 1980, found that only 5% of cases of violence against staff were reported.

Relationship between broadly defined mental disorder and violence (Walsh and Fahy, 2002; see also Wallace ea, 2004; Friedman, 2006; Swanson ea, 2008; Large ea, 2008)
Modest relationship between psychosis and violence
Untreated schizophrenia, major depression, and bipolar disorder
Anxiety disorders not associated with violence
Greatest risk is with personality disorder, drug abuse, and the severely mentally ill who also misuse drugs
Being male, young and poor contribute more to violence than does mental disorder

Not all violence committed by the mentally ill stems from their psychiatric disorder
 Falling UK homicide rate despite communitisation **or** rise in homicides attributed to mental disorder to mid-1970s in England and Wales followed by a fall whilst other homicides continued to rise
 Victim of violence against self in the past
 Homelessness
 Poor medical health
 According to the RCPsych (1996) about 100 homicides each year were committed in England and Wales by people judged to be mentally abnormal at the time of the act
 Rise in homicide by schizophrenic patients in one part of Australia paralleled a general increase in societal violence
 Total number of homicides and those attributed to mental disorders³⁸⁸⁷ in England and Wales rose steadily until mid-1970s but those attributed to mental disorders fell after 1981 to early 1950s levels (Mayor, 2008)

The fact that a patient has a lifetime history of schizophrenia does not automatically mean that diagnosis explains homicide.(Shaw ea, 2006) Mullen (2006) reminds us that schizophrenic patients do kill others and that we cannot underestimate its impact on others.(see also Dean ea, 2008)

Serious violence following threats to kill (Warren³⁸⁸⁸ ea, 2008)
 10 year review of 613 people **convicted** of threats to kill
 2.6% (16) committed suicide³⁸⁸⁹
 3 were murdered
 44% convicted of further violent offending, including 3% homicides
 History of psychiatric contact at time of index offence (40%) was associated with higher rate (56%) of subsequent violence
 Highest risk factors: drug misuse, mental disorder, youth, and no prior criminal conviction
 Most frequent association with homicidal violence: schizophrenia

It is important that psychiatrists do not overstate their capacities to predict or prevent dangerousness.(Mullen, 2000) Doyle and Dolan (2006) suggest that current social functioning, mental state and contextual factors, backed up by measures such as the *Historical Clinical Risk – 20 items scale* (HCR-20³⁸⁹⁰: Webster ea, 1997; Gray ea, 2008), assist the clinician in rationally estimating risk of community violence in discharged patients.

Violence: Repetitive acts of violence are associated with an increased incidence of abnormal brain function as shown by neuropsychological tests, EEG and CT scan.(e.g. Krieger, 1985) These abnormalities tend to be located mainly in three brain areas: frontal cortex, amygdala, and temporal cortex. These cerebral regions coincide with the areas indicated in the genesis of aggression in animal studies. PET scans may reveal abnormalities in the left temporal lobe of patients with a history of repetitive, purposeless violence,(Volkow & Tancredi, 1987) and a lifetime history of aggressive impulsivity may relate to prefrontal metabolic abnormalities (negatively correlated with regional cerebral glucose metabolic rate) on PET scanning in patients with personality disorders.(Goyer ea, 1994) Volkow and Tancredi (1987) discuss three basic syndromes associated with

³⁸⁸⁷ Homicides attributed to mental disorders = not guilty by reason of insanity, diminished responsibility, unfit to plead, infanticide, or offender committed suicide around same time as homicide.

³⁸⁸⁸ Australian study, including P E Mullen.

³⁸⁸⁹ Asnis ea (1997) reported that 91% of outpatients who had attempted to kill another person had also tried to kill themselves and that 86% of patients who had thoughts of killing others also thought about suicide.

³⁸⁹⁰ See earlier.

neurological impairment and violence: the prefrontal area³⁸⁹¹, limbic areas³⁸⁹², and association areas³⁸⁹³. The medial frontal cortex (on MRI) may be excessively thin in violent people with antisocial personality disorder. (Narayan ea, 2007) Poor (electrodermal) fear conditioning at age 3 years was prospectively found to predispose to crime at age 23, suggesting a neurodevelopmental aetiology. (Gao ea, 2010) High serum or salivary testosterone levels have been linked with violent crimes. Murderers with sociopathic personalities may have sub-sensitive serotonergic systems. (O'Keane ea, 1992) An excess of vasopressin may have a role in aggression. Violence may occur in patients on high doses of antipsychotic drugs, e.g. haloperidol 60 mg/day. (Herrera ea, 1988)

Neurobiological basis of violence (Siever, 2008)

Neurobiological susceptibility more likely with repeat offenders
 'Top-down' control systems (prefrontal cortex, PFC) fail to modulate aggressive acts triggered by anger provoking stimuli
 Imbalance between PFC inhibitory influence and hyper-responsive amygdala and limbic regions with role in affective evaluation
 Lack of 5-HT facilitation of 'top-down' control
 Excess stimulation by catecholamines
 Subcortical glutamine/GABA imbalance
 Abnormal neuropeptide systems

Women are at particular risk of male violence. (Clare, 2000; but see Home Office, 1998 above) Men who are more controlling are more likely to be violent against their partners; and variation in prevalence around the world suggests that such violence is not inevitable. (Garcia-Moreno ea, 2006)

Intermittent explosive disorder³⁸⁹⁴

In DM-IV section on 'impulse control disorders not elsewhere classified' (diagnosis of exclusion)
 Syndrome with long and controversial history (Mullen, 2000)
 Discrete episodes of failure to resist aggressive impulses (loss of temper) leading to serious assaults/destruction of property
 Starts in adolescence or early adulthood and may diminish in intensity in the twenties; there may be a history of child abuse
 Medical help tends to be sought only when there are adverse consequences of temper outbursts
 Are such patients prone to react to narcissistic injury, real or imagined?³⁸⁹⁵
 Behaviour not explicable by another diagnosable condition
 Reported by 2.6% of population (12-month prevalence rate) in National Comorbidity Study replication (Kessler ea, 2005)
 Is it a disorder of personality (cluster B)?
 Form of epilepsy?³⁸⁹⁶
 Another Axis I disorder?³⁸⁹⁷

³⁸⁹¹ Higher cognition: consciousness, abstraction, etc. Possibly unable to understand right from wrong or to appraise the consequences of a violent act.

³⁸⁹² Generation of affects and emotions: do feelings arise spontaneously with associated outbursts of rage and violence and poor impulse control? May have an excess of EEG abnormalities.

³⁸⁹³ Derangements in perception could evoke assaultive behaviour when a stimulus is perceived as threatening.

³⁸⁹⁴ The old 'episodic dyscontrol syndrome'.

³⁸⁹⁵ Threats of attack, abandonment, rejection, or other blows to self-esteem have been suggested.

³⁸⁹⁶ EEG abnormalities are non-specific, mild abnormal neuropsychological findings (e.g. letter reversal), and neurological soft signs have been reported. Low CSF and platelet 5-HT levels have been reported.

³⁸⁹⁷ Patients themselves and their close relatives may have an excess of drug use or affective disorders.

Is it one end of a continuum with normality? (Lambert et al., 2003, pp. 1108-9; Cohen, 2003, p. 454)

Selected reported associations with violence

1952. Denis Hill reports on EEG in psychopaths.

1963. Bandura reports that aggressive models increase the likelihood of aggression in children.

1969. Williams confirms Hill's EEG findings. He also showed that among males convicted of violent offences those with habitual aggressiveness had abnormal EEGs (esp. anterior temporal) whereas those with single aggressive outbursts more usually had normal EEGs and the outbursts were usually environmentally provoked.

1983. Pfeffer and others report that aggression in parents strongly predicts aggression in their children.

1987. Volkow and Tancredi, using PET, reported abnormal metabolism in frontal and temporal areas in males with personality disorder.

1988. Lewis and co-workers report that CSA and physical abuse in childhood is common in the histories of criminals.

1990. Looked at > 9,000 crimes in 11 countries; 2 out of 3 violent offenders were drinking alcohol at the time of the crime, and almost half of the victims were intoxicated when victimised.

1992. The more aggressive rhesus monkeys had low CSF 5-HIAA and high CSF noradrenaline. Males often die early and females occupy low positions in their troops. Being reared by peers rather than the mother is associated with low 5-HIAA levels.

1993. Most assaultive psychiatric inpatients: bipolar disorder, personality disorder, and chronic organic mental disorders.

Homicide in US homes associated with: illicit drug use, a history of physical fights at home, or having guns in the house.

1994. Conflicting evidence to suggest that lowering cholesterol levels may lead to violence, possibly by reducing brain serotonin levels.

Based on eyewitness accounts, violent incidents involving psychiatric hospital inpatients are most commonly preceded by (a) agitated/disturbed patient, (b) restrictions placed on patient by hospital regimen and (c) provocation by other patients/relatives/visitors. Incidents arising from staff members initiating contact with patients were very rare.

Male rhesus macaques (*Macaca mulatta*) with reduced CSF 5-HIAA levels show more violent forms of aggressive behaviour and greater risk taking.

Murderers had reduced metabolism on PET in lateral and medial prefrontal cortex compared to controls. Goyer and co-workers, using PET, found that the lower was glucose metabolism in the frontal cortex of personality disordered persons the more likely was there to be a history of aggression.

1996. Shooting of children by other children is a major problem in the USA.

Finnish study of homicides found that schizophrenia without alcohol disorder increased homicide risk 7 and 5 times for males and females respectively; if with alcohol disorder these figures climbed to 17.2 and 80.9 respectively.

1997. Substance abuse associated with greater risk of violence on the part of patients in an American private psychiatric hospital.

Flunitrazepam (Rohypnol), especially when combined with illicit drugs was associated with date rape (as is gamma-hydroxybutyrate); banned in US; Roche Pharmaceuticals changed the formulation in the hope of reducing misuse.

Psychopathy associated with different pattern of relative cerebral blood flow than seen in controls when processing emotionally laden words.

PET study of males with schizophrenia and schizoaffective disorder found reduced glucose uptake in right plus left anterior inferior temporal lobes in non-repetitive offenders but only on left side in repetitive offenders.

1998. Non-compliance plus alcohol/drug abuse in seriously ill patients is associated with serious violence in the community.

Young male Finnish schizophrenic males who abuse alcohol are 25.2 times more likely to commit violent crimes than are normal men; non-alcoholic males with mental illness only 3.6 times more likely to commit violent crimes than are normal men.

Decreased prefrontal regional cerebral metabolic rates for glucose in murderers, especially in ventromedial brain regions, especially in those patients from stable backgrounds – suggesting genetic rather than environmental input.

1999. Americans want childproof handguns and personalised weapons (activated by fingerprint or code)!

Maternal smoking during pregnancy associated with violent offences in offspring only if the offspring experienced delivery complications.

Maternal smoking during pregnancy associated with violent offences in offspring if mother was a single teenager who did not want the pregnancy or if developmental motor lags occurred.

Low cholesterol associated with impulsivity in personality disordered people

2000. Increased rates of offending in the community (Victoria, Australia) by schizophrenic patients parallels that in the general population.

In DSM-III-R patients with various diagnoses, reduced CSF 5-HIAA levels are associated with aggressiveness regardless of suicidal behaviour.

The US Brady Handgun Violence Prevention Act of 1994 may have reduced the use of such weapons for suicide purposes in older people but has not reduced either the homicide rate or overall suicide rates. People have observe a waiting period before buying a gun while their background is being checked; and illegal sources of guns are difficult to check reliably.

No evidence for an association between recorded adolescent psychopathology and criminally violent behaviour. The latter was associated with a history of emotional or physical abuse, contact with social or mental health services, and previous criminal behaviour.

11% reduction in prefrontal grey matter volume on MRI in males with antisocial personality disorder.

Violence is easiest to enact when one dehumanises the object of anger.

Low cholesterol associated with aggressiveness/impulsivity in personality disordered people

Mild intellectual disability is associated with higher rate of offending compared to normal IQ peers; more severe intellectual disability is rarely associated with serious crimes

2001. Clozapine is superior to haloperidol and risperidone for aggression in schizophrenia.

Offenders with borderline personality disorder and those with repeated self-harm or alcohol misuse had low 5-HT function. 5-HT function inversely correlated more with impulsivity than with aggressive acts. Plasma testosterone is associated with aggressive acts. Psychopathy is associated with lower initial cortisol and higher testosterone concentrations.

Repetitively violent alcoholics with antisocial personality disorder showed a negative correlation between dorsal hippocampal volume and psychopathy score; since hippocampus is involved in fear conditioning, is there a problem in neural circuit involving prefrontal and temporolimbic areas?

High activity COMT homozygosity in schizophrenia may be associated with more aggression (the COMT gene inactivates catecholamines).

Women who are abused in childhood are at risk of domestic violence in adulthood.

2002. PET study suggests that diminished activation of inhibitory regions of the brain (e.g. anterior cingulate) in impulsively aggressive patients in response to a serotonergic stimulus, m-CPP, may contribute to poor modulation of aggressive impulses.

2003. Childhood psychotic symptoms (and, to a lesser degree, childhood physical aggression) were a strong risk factor for violence in adults with schizophreniform disorder.

2004. Being on an atypical (v conventional) antipsychotic may be more likely to reduce violence among community-based schizophrenic patients.

16% and over one-tenth of all violent crimes in Sweden during 1988-2000 were committed by people with hospital discharge diagnoses of alcohol abuse and drug misuse respectively.

Swedish study suggests that previous studies have underestimated psychiatric morbidity in homicide offenders: 20% were psychotic and 54% had a personality disorder.

2005. Meta-analysis showed that violence in the visual electronic media increases short-term aggressive and fearful behaviour in younger children, especially in boys; evidence for long-term is inconsistent.

2006. Swedish study found population attributable risk fraction ³⁸⁹⁸ of 5.2% for severe mental illness on violent crime, higher in women than in men.

Dopaminergic transmission is implicated in aggression/hyperactivity and such externalising behaviour is negatively associated with cognitive ability; in people lacking a 7-repeat allele in third exon of D4 receptor gene externalising behaviour negatively correlated with IQ, whereas in those with at least one copy externalising behaviour and IQ did not correlate.

2007. Patients discharged from medium secure forensic psychiatry services: most were not subsequently convicted; patients with pre-admission convictions were at highest risk of violent reconviction.

2008. Genes and environment interact in complex ways to produce externalizing behaviour.

US children are more aware of location of household guns/ammunition than parents realise.

Approaches to reducing violent tendencies include mood stabilisers to dampen limbic irritability, SSRIs to enhance top-down control, teaching alternative coping strategies, and re-inforcing reflective delays ³⁸⁹⁹. (Siever, 2008)

Handling emergencies³⁹⁰⁰ (RCPsych, 1998): Always have enough hands to restrain the patient comfortably. Do not confront. If the patient is armed and is unwilling to put it in a neutral location³⁹⁰¹ with a dangerous weapon call the police and stay clear. Avoid drugs in those who are intoxicated. A shared cup of tea and a calm chat sorts out many

³⁸⁹⁸ Population attributable risk fraction = proportion of violent crimes in the whole population that may be attributable to individuals with severe mental illness.

³⁸⁹⁹ During the early 1980s the author prescribed clopenthixol depot injections for a young man who had recently begun hitting his wife without warning whilst watching TV. After a couple of weeks the patient told the author that 'this drug is great. I feel like hitting her but it makes me stop and think about it. But then I hit her anyway!' Unfortunately the man turned out to have a malignant primary cerebral tumour which caused prolonged coma before he died.

³⁹⁰⁰ Sedation is covered under common law in any setting. It is specifically covered under the *Mental Health Act 1983* for informal patients in England and Wales. It should be noted that the making of a contract with a patient that he or she will do no harm to him/herself provides no medico-legal protection – a comprehensive assessment (documented in the notes) should not be omitted.

³⁹⁰¹ Do not ask an armed patient to hand a weapon directly to you.

problems. Oral medicines (e.g. olanzapine velotabs) are generally safer than parenteral drugs. Examples of emergency drugs include olanzapine as velotabs or (see below) IM, lorazepam 2-4 mg IM³⁹⁰² (McAllister-Williams & Ferrier, 2002), haloperidol 5-15 mg IM or slowly IV³⁹⁰³, haloperidol (10 mg) plus promethazine³⁹⁰⁴ (Phenergan, 25-50 mg) IM, (Alexander et al, 2004; Raveendran et al, 2007; Huf et al, 2007) or clopenthixol (Acuphase) 25-100 mg IM every 3 days. (see also Raveendran et al, 2007) Oral medications are safer than parenteral ones, e.g. lorazepam 2-4 mg plus risperidone 1-2 mg every 8 hours. In one study (Currier et al, 2004) risperidone 2 mg and lorazepam 2 mg given orally was as effective for psychotic agitation as was haloperidol 5 mg plus lorazepam 2 mg given IM. Compliance is increased with use of syrup. Lorazepam (Ativan) has a half-life of 12-14 hours, it acts quickly, and is better absorbed from IM sites than is diazepam. (Tardiff, 1996) It is preferred (as is oxazepam) in cases with hepatic impairment and when predictable elimination is desirable³⁹⁰⁵. Lorazepam, which has no active metabolites, is metabolised by kidney and liver.

Tyrer et al (2008) found that risperidone, haloperidol, and placebo each decreased aggression in non-psychotic intellectually disabled patients substantially by four weeks. They hold that antipsychotic drugs should not be given routinely in such circumstances. This is not a total prohibition. Whilst behavioural interventions are ideal, staff may be neither trained or willing to become involved. (Matson & Wilkins, 2008)

Olanzapine (Zyprexa IM: 10 mg Powder for Solution for Injection) is an IM preparation for use in the acutely agitated psychotic patient. 10 mg of this is roughly equivalent to 7.5 mg haloperidol in reducing agitation, measured 2 hours after administration. The effects last about a day. It should only be given intramuscularly, never IV or SC. It can be given on a maximum of 3 consecutive days. The starting dose is 10 mg (elderly or in people with hepatic or renal impairment = 2.5-5 mg). A second injection of 5-10 mg can be given 2 hours later if necessary. The maximum daily dose is 20 mg (combined oral plus IM). No more than 3 injections should be administered over a 24-hour period. These instructions should be strictly adhered to.

Dealing with a violent patient

Anticipate problems – hostility, agitation, restlessness, abusiveness, or lack of control.

Do not sit behind desk – sit nearer than patient to an open door.

Don't be angry/threatening/patronising.

You should not approach the patient too quickly – respect personal space.

Check your gut feeling³⁹⁰⁶ – feel scared? Do not interview alone. Ask the patient if he has a weapon on his person and have it removed.

Offer anything reasonable – assistance, food, medication – praise patient for strength and self-control.

Should restraint be required: hold hands/arms/legs; do not restrain without sufficient help; be kind/firm; one person should co-ordinate all; and do not bargain; search for drugs/weapons/syringes.

If oral medication is refused offer an injection and give injection if patient still refuses.

³⁹⁰² 4 mg/ml ampoule.

³⁹⁰³ Very high doses may rarely cause arrhythmias, including *torsade de pointes*. If haloperidol is given by IV line, the latter should be flushed with saline first, because heparin may precipitate heroin within a vein. **DO NOT USE** haloperidol in an emergency unless reasonable (and documented) efforts are made to outrule any cardiac risk factors; get an ECG as soon as possible – if there is a prolonged QTc check serum magnesium level; olanzapine is probably a safer option (although this author has used parenteral haloperidol for many years without mishap!); when in doubt use benzodiazepines for the moment and monitor in the recovery position for respiratory depression. It has been suggested that IV haloperidol causes less EPS than when it is administered orally. (Menza et al, 1987)

³⁹⁰⁴ A Vermont guitarist (Diana Levine) won damages in 2009 because the US Supreme Court found that the manufacturer's labelling on Phenergan wasn't strong enough in warning of the danger of gangrene and amputation from inadvertent intra-arterial injection. The patient argued that labelling should have advocated that an IV drip be employed instead of a direct IV injection.

³⁹⁰⁵ E.g. the delirious, medically ill patient.

³⁹⁰⁶ Your 'psychoscope'.

Observe patient carefully if sedated/restrained – do not leave him alone.
 Consider admission if the patient intends to harm anyone (or won't discuss this), is abusing drugs/alcohol, is psychotic/cognitively disordered/will not or cannot co-operate with treatment.
 Should there be a potential victim you have a duty to warn directly or via police – this includes staff.
 Follow up observation (frequency and nature stated clearly in writing) and documentation.
 Get information from informants.
 Never forget to look for an organic aetiology.

Seclusion

Seclusion has been used in psychiatry for many years, an early advocate being Cullen in the early 19th century. Published research in the use of seclusion often failed to offer consistent guidelines for its use. (Angold, 1989) It should be supervised by senior staff and subject to frequent appraisal. Details of why it is being used, on whom, its form and duration, its effects, and what use of it has been made in the past and what were its effects, should be recorded. A regular medical review of secluded patients is essential. It should not be used as a punishment or to obviate staff shortages.

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31

Rehabilitation in psychiatry

32

A Short History of Psychiatry

Brian O'Shea

'It is a matter of history that psychiatry as we know it has developed as a branch of Western medicine'. (Mumford, 1999)

'Gone is the image of the madman with the strength of ten: it seems that the image of madness in the twenty-first century will rather be one of dilapidation and waste'. (Tantam, 1999)

'The asylum was not instituted for the practice of psychiatry; psychiatry rather was the practice developed to manage its inmates'. (Porter, 2002)

*Psychiatry*³⁹⁰⁷ is in the broadest sense is as ancient as insanity and has provoked varied social attitudes and responses. (Porter, 2002) When doctors began to discover that certain types of brain dysfunction could be associated with physical signs and discernible brain changes some broke away from psychiatry to become neurologists, leaving alienists ('mad doctors', psychiatrists) to manage idiopathic disorders with no known cure³⁹⁰⁸. Skulls have been trepanned³⁹⁰⁹ since about 8000 BC. It may be that our ancestors wanted to release



spirits causing madness or epilepsy, although they could have been treating depressed skull fractures. Ancient China had institutions for the insane whose inmates remained until they regained lucidity. Yoga, from Vedic India, prescribed measures for the development of a mature personality. Magic played a central role in aetiological and therapeutic considerations until relatively times. Both religion and physical therapy co-existed harmoniously in ancient Memphis *circa* 3000 BC. According to Homer³⁹¹⁰, illness is based on man as a social creature. In Homer's, the heart was the seat of the emotions, intellect and will, moving to the brain in Hippocratic times³⁹¹¹. (Berrios & Mumford, 1995) Hippocratic medicine owes much

to the earlier rationalism of natural philosophers from the Ionian city of Miletus. (Longrigg, 2001, p. 28) According to the latter³⁹¹², the environment is explicable in physical terms and a supernatural explanation is not required. In other words, disease is impersonal. During mummification in ancient Egypt, the heart, regarded as the seat of the mind, was left inside the body, whilst the brain was pulled out through the nose

³⁹⁰⁷ *Psyche*, mind; *iatros*, a healer. The term was coined by the German professor of medicine Johann Christian Reil (1759-1813) in 1808. Reil was professor in Halle and later on in Berlin. He died of typhus. Heinroth was appointed to the first chair of psychiatry in 1818. (Leipzig) Von Feuchtersleben introduced the term psychosis in 1844.



Johann Christian Reil

The term 'forensic' comes from the fact that criminals were tried in the ancient Roman *forum*. Roman law held that insane people could not form a malicious intent.

³⁹⁰⁸ This accounts in part for the long delay in establishing psychiatry as a discipline with scientific leanings. (Häfner, 2002)

³⁹⁰⁹ Trepanned with sharpened stone tools.

³⁹¹⁰ 8th century BC - of *Iliad* fame.

³⁹¹¹ 5th century BC.

³⁹¹² 6th century BC.

with a hook. The gods measured moral worth by the weight of the heart. (Magner, 1992, pp. 24 & 34) The most famous temple of physical and mental³⁹¹³ healing in ancient Greece was at Epidaurus, which was associated with the god of healing, Asclepius³⁹¹⁴. A brief stay in a culturally valued, non-threatening healing temple is still likely to improve psychopathology in today's India. (Raguram et al, 2002) The *Talmud* recognised the existence of mental illness and the *Koran* enjoins us to treat the insane with humanity and care. Moses, in *Deuteronomy*, warns his flock that failure to heed God's laws will cause Him to 'smite you with madness and blindness and confusion of mind.' Aretaeus of Cappadocia³⁹¹⁵ gave a vivid description of melancholia³⁹¹⁶ in *On the Causes and Signs of Diseases*. He is said to be the first to stress the disturbance of sleep in that condition ('...start up from a disturbed sleep', although Job beat him to it³⁹¹⁷) and is often credited with identifying what would later be known as bipolar affective disorder³⁹¹⁸. Maimonides (1138-1204) was a Rabbi and physician who gave an early description of psychosomatic medicine. Interestingly, he prescribed alcohol for depression, even for Muslims!³⁹¹⁹ Maimonides was a strong believer in patient autonomy despite living in an era of paternalism. (Gesundheit et al, 2008)

Britain & the wider World³⁹²⁰

'As a professional discipline, psychiatry in Britain in Victorian times – if it existed at all – was in an embryonic state'. (Rollin, 2003)

Roman law dictated that authority over a lunatic and his goods belonged to either the paternal line or to the clan, and laws relating to such apparently modern concepts as testamentary capacity were well developed. A return was made to demons and the casting out of evil influences by violent means as the Empire collapsed. A hospital for the mentally and physically infirm was founded at St. Alban's in the last decade of the eighth century by visiting monks. Lessons learned during the Crusades led to the acknowledgement of a difference between psychic and external causes of lunacy.³⁹²¹ A special ward for the insane could be found in a hospital built by al-Mansur in Cairo in 1283 (Udwadia, 2000) with soporific music and distracting tales providing much of the therapy.

First asylums in Continental Europe (Stone, 1997)

Granada, 1365
Hamburg, 1375
Valencia, 1410

Friar Jofré (1350-1417) was so incensed by the public ridicule of the mentally ill that he campaigned for the building of a mental asylum. With monies from local merchants the construction of the Hospital for Lunatics, Insane and Innocents (*Spital Dels Folls, Orats, e Ignocents*) began in 1410 in Valencia, Spain. (Aldana et al, 2010)

St. Mary of Bethlehem (Bethlem, Bedlam) Hospital, a priory³⁹²² until 1375, was founded at Bishopsgate³⁹²³, London in 1247. It moved to Moorfields³⁹²⁴ in 1676, to Lambeth³⁹²⁵ in 1815, and finally to Beckenham in Kent. (Russell, 1997) As mentioned in Shakespeare's *King Lear*, inmates had to beg in the streets: *Tom-o'-Bedlams*. Its early history makes for disturbing reading. (Arnold, 2008, e.g. p. 192) It is interesting that these beggars simulated mental illness using symptoms very similar to what we now call

³⁹¹³ L. *mens* = mind.

³⁹¹⁴ Also known as Aesculapius.

³⁹¹⁵ Lived c.150-200 AD.

³⁹¹⁶ *Melan*, black; *khole*, bile.

³⁹¹⁷ '...nothing of my own but nights of grief. Lying in bed I wonder, "When will it be day?" Risen I think, "How slowly evening comes!"' (See *Job* 7: 1-4, 6-7.)

³⁹¹⁸ Falret's *folie circulaire* and Baillarger's *folie à double forme*.

³⁹¹⁹ See *Koran* prohibition on alcohol: 2:219;5:90-91.

³⁹²⁰ Because British law applied to Ireland until the 1920s, unless otherwise stated this section focuses on British history.

³⁹²¹ 'Lunacy' refers to the belief that the moon affects our minds, e.g. a full moon causes madness or the mad become disturbed during a full moon. There is evidence against such a malign influence. Early negative research was reported by the Bethlem apothecary John Haslam (1764-1844) in 1809. O'Shea (1989) found that a belief in a lunar effect was brought into psychiatric nursing but that it waned with experience.

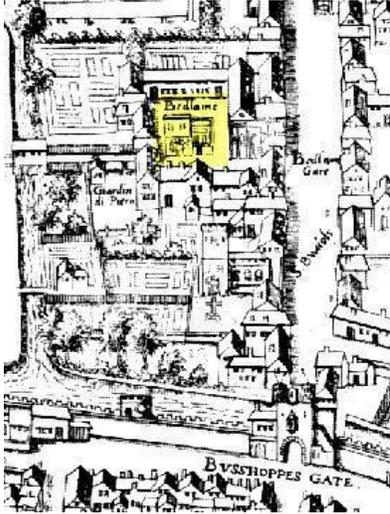
³⁹²² Order of the Star of Bethlehem.

³⁹²³ Now Liverpool Street Station.

³⁹²⁴ Mary Lamb killed her mother in 1796 and was placed in Bethlem. She and her brother Charles would become famous for their *Tales from Shakespeare*.

³⁹²⁵ Now the Imperial War Museum.

schizophrenia (Turner, 2010, p. 7), possible evidence against the Fuller Torrey and Miller (2001) theory that schizophrenia is a consequence of modern industry-driven urban living.



Bedlam map about 1558

Lieutenant David Davis shot at Henry John Temple (Lord Viscount Palmerston, War Secretary) on April 8 1818 and was committed to Bethlem on May 1818 from which he sent his auto-amputated penis to Palmerston! Scotland's first mental hospital was founded in 1781 by Mrs Susan Carnegie: the Montrose Lunatic Hospital³⁹²⁶. The Narrenturm³⁹²⁷ of Vienna was built in 1784. An 1812 inscription on the foundation stone of Dundee Lunatic Asylum³⁹²⁸ read: 'To restore the use of reason, to alleviate suffering and to lessen peril where reason cannot be restored'.



Narrenturm

The manner in which the insane were treated varied from incarceration to canonisation³⁹²⁹. Medicine took a detour when it came to mental illness, madness becoming the business of priests. The *Papal Bull* of Innocent III in 1484 gave birth to the Inquisition to be 1489 by *Malleus Maleficarum*³⁹³⁰ composed by the monks Sprenger and Kraemer, a guide to witch identification³⁹³¹. (Baigent & Leigh, 1999) The rare medical man protested the spiritual innocence of epileptics or melancholics. Moslems built special facilities for the mentally ill and employed diets, baths, perfumes, drugs and entertainment in their treatment. Emergence from the Dark Ages led to changed ideas concerning the origins of madness. The *Poor Law Act*, 1601, held pauper support to be a parish responsibility, destitute lunatics included. However, ways were devised to decrease the likelihood of people seeking aid from the parish: they could be thrown out of the parish and so become someone else's problem or they could be housed in one of the new and inhospitable

³⁹²⁶ Later the Royal Scottish Asylum.

³⁹²⁷ German: 'lunatic's tower'.

³⁹²⁸ The asylum was opened in 1820/1 with 50 inmates, the latter rising to 300 in the late 1870s.

³⁹²⁹ James Norris, confined in Bethlem from 1804-1813, was riveted into an iron harness and chained to a post by an iron collar. The great witch-hunts of the Inquisition found many victims among the mad. This was a time of mass hysteria in nunneries and the whipping of the base flesh.

³⁹³⁰ 'Hammer of Witches': this notes that Irish fairies are generally benevolent creatures! See section on the German physician Johannes Weyer.

³⁹³¹ King Coloman 'the Scholar' of Hungary (ruled 1095-1116) banned inquisition against witches since 'no such creatures exist'. (Csorba et al, 2003, p. 30) Laws prescribing the punishment of witches in England were repealed in 1736.

1180

workhouses. Vagrant paupers were placed in Bridewells³⁹³² if they refused to work. If a madman broke the law he was cast into prison. Better-off lunatics were boarded out with doctors or priests. Private lunacy houses³⁹³³ were developed eventually and provided a high percentage of places for the confined mad in England for many years. These were outside the law with the lunatic inmate at the proprietor's mercy. It was in the second half of the 17th century that Bedlam earned its infamous title. (Porter, 2004, p. 128) The inmates were prodded by paying visitors through bars³⁹³⁴, a practice that lasted up to circa 1770³⁹³⁵. (Porter, 2001a, p. 94) Some lunatics who remained at home were chained in outhouses under conditions more reminiscent of chicken runs.

The second half of the 18th century saw the opening of public madhouses. Interventions now offered to madmen make for strange reading today, e.g. ice-cold baths, leeches, phlebotomy, stretching on the rack, and scarification. These approaches were little different from those used in other branches of medicine. (e.g. Robins, 1995, p. 48) Opinions on the benefits of bloodletting varied within medicine, William Battie (1703-1776) of St Luke's stating it to be harmful in *A Treatise of Madness*, and John Monro (1715-1791) of Bethlem praising its usefulness in his *Remarks* on Battie's treatise (The Monro dynasty at Bethlem spanned four generations: James, John, Thomas, and Edward, with a fifth generation, at St Luke's Hospital for Lunatics³⁹³⁶ and Brooke House Asylum in Hackney, represented by Henry.).

In 1791 Philippe Pinel struck the chains³⁹³⁷ from the male inmates of *Le Bicêtre* in Paris; he did the same for the women of the *Salpêtrière*³⁹³⁸ a few years later.



Salpêtrière

Together with his fellow Quakers, William Tuke³⁹³⁹ (1732-1822), upset by what passed as therapy for the insane, opened *The Retreat* at York in the last decade of the 18th century; the theoretical model employed, a type of humanistic Christianity, was called 'moral' treatment.



York retreat

A 1763 Select Committee of the House of Lords reported that some asylum admissions were purely an answer to family and social problems³⁹⁴⁰. (Leigh, 1961)

³⁹³² The original Bridewell, a house of correction, was in London. The name stuck elsewhere, including in Dublin.

³⁹³³ 'Trade in lunacy'. The English *Vagrancy Act*, 1744, distinguished between lunatics and paupers, thereby spurring the development of the private asylum. Inmates either paid themselves or were funded by parishes.

³⁹³⁴ Lunatics were displayed in wooden cages for the amusement of paying visitors in Vienna until the mid-19th century. (Moussaoui, 2002, p. 60)

³⁹³⁵ Public executions at Tyburn continued until 1783.

³⁹³⁶ Founded 1751.

³⁹³⁷ Largely figuratively. (Duffin, 2000)

³⁹³⁸ Built as an arsenal in the early 17th century, later an asylum for beggars, prostitutes and insane; largest poorhouse for women.

³⁹³⁹ A retired tea merchant, Tuke and others were dismayed by the poor treatment and demise of a Quaker from Leeds (Hannah Mills, a melancholic) in the York Asylum in 1790.

³⁹⁴⁰ An early version of the 'gaslight' phenomenon or an acknowledgement of Michel Foucault's (Foucault, 1961) 'great imprisonment of madness' (also called the 'great confinement') aimed at excluding the unruly insane? Second sons were over-represented in Irish asylums probably because of lack of prospects, frustration, and alcohol abuse. López-Ibor (2002, p. ix) points out that asylums were a repository for people deemed a nuisance to society.

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The *Criminal Lunatics Act* of 1800 was unsatisfactory. A subsequent official enquiry led to recommendations for the setting up of county asylums. The asylums were to be financed by local rates and admissions and discharges were to be under legal control. The disposal of criminal lunatics³⁹⁴¹ remained problematic: the first provision for this group consisted of a special wing at Bethlem Hospital³⁹⁴² under Home Office control. Ireland's Central Mental Hospital at Dundrum opened in 1850. Broadmoor Hospital in England was opened in 1863.

The *County Asylum Act* of 1808 gave rise to many large mental institutions³⁹⁴³. Early asylums³⁹⁴⁴ were relatively cheap to build, the general standard of living being low. Paying patients might be admitted in order to lower rates on the county and the physician was paid on a *per capita* basis. Until well into the nineteenth century, physicians were confined to treating the physical ailments of inmates. (Häfner, 2002) An early distinction arose between short-stay wards and 'back wards'. (Jones, 1991) Outrage at the conditions of inmates³⁹⁴⁵ led to the formation of visiting committees (justices) reporting to the Home Department.

The first American insane asylum was at Williamsburg, Virginia (1773). Moral treatment³⁹⁴⁶, a lay-instigated and non-medical approach characterised by 'gentle humanitarianism coupled with enlightened rational optimism', (Goldstein, 2004) was employed at the Friends Asylum for Persons Deprived of the Use of their Reason, built in 1813, the first private American asylum. Thomas B Kirkbride (1809-1883), an important figure in the early Association of Medical Superintendents of American Institutions for the Insane³⁹⁴⁷, trained at Friends. Kirkbride, influenced by Dorothea Dix, wrote *On the Construction, Organization and General Arrangements of Hospitals for the Insane* (1880) and viewed asylum care as superior to "inhumanity and barbarity"³⁹⁴⁸.



Dorothea Dix (1802-87)

The New Hampshire Asylum for the Insane, founded in 1842, had many patients with diagnosed "religious excitement", which did not prevent their being treated with obligatory attendance at religious service! Clifford Beers, a former patient, exposed the wretched living conditions of American asylum residents in 1908. He, Adolph Meyer, and William James founded the National Association for Mental Health in 1909.

³⁹⁴¹ Those insane who had fallen foul of the law.

³⁹⁴² It opened in 1816 following the firing of shots at King George III by Hadfield in 1800. Hadfield was found not guilty by reason of insanity. Physical treatments such as cold baths and drugs were also used.

³⁹⁴³ English and Welsh county and city asylums contained just over a thousand inmates in 1827, increasing to 77 asylums and over 74,000 inmates in 1900. During the same period the average number of inmates in an asylum jumped from 116 to 961. (Andrews, 2004, p. 302) By 1944 there were 17 public county asylums, 11 mixed public-private asylums, and 139 private licensed houses. (Andrews, 2004, p. 301)

³⁹⁴⁴ "Stately homes for the lower classes". James and Barrett (2007) make the point that the asylum inmate was further isolated by the fact that asylums were built in the countryside when the rural population were fleeing to cities. They also say that isolation is compounded today by residence in suburbia which empty during working hours!

³⁹⁴⁵ Historical judgements on the living standards in asylums often conveniently forget the abysmal living standards of most citizens that existed up until recent times. (cf. for example Robins, 1980, 1995) This is not to say that they were ideal, far from it. (Robins, 1993, p. 120) For rules governing approved centres in the Republic of Ireland see *Mental Health Act 2001 (Approved Centres) Regulations 2006*.

³⁹⁴⁶ Meaning psychological/non-somatic but with moral undertones: included in the package might be isolation from external sources of stress, questioning of aberrant thinking, physical restraint, entertainment, etc.

³⁹⁴⁷ 13 superintendents met at Jones Hotel in Philadelphia in 1844 to form this organisation, its first president being Samuel Woodward of Worcester, Mass. It would become the American Medico-Psychological Association (MPA) in 1893, and the American Psychiatric Association (APA) in 1921. (Butler, 1887)

³⁹⁴⁸ Oregon State Hospital, 1883-2008, developed its asylum milieu based on Kirkbride's ideas of moral treatment. It was the location for the movie *One Flew Over the Cuckoo's Nest* (1975), based on the book by Ken Kesey (an Oregonian) who had at a Californian VA hospital. Cremated remains of thousands of former inmates were kept in storage room and discovered in 2004! (Lazarus, 2009)



Adolf Meyer (1866-1950)

The use of pet animals for the comfort of patients in 19th century asylums continues to find advocates. (Allderidge, 1991)

In the 1830s the total abolition of restraint was advocated by John Conolly (1794-1866) at Hanwell Asylum, itself opened as the result of the exposure of brutal practices elsewhere. It was Conolly who was responsible for the opening of Colney Hatch Asylum in 1849³⁹⁴⁹. There, medical duties were divided between administration and the classification of inmates.

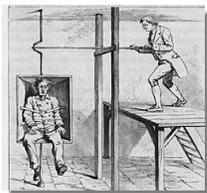


John Conolly

The *Madhouse Act* of 1828 sought to prevent collusion between the certifying physician and the owners of asylums. The *Lunacy Act* of 1845 gave birth to a National Lunacy Commission with responsibility for all types of institutions throughout the country, from prisons to madhouses. Few asylums were built after 1920³⁹⁵⁰.

A Swiss doctor, Guggenbuhl, founded the first special residential institution for the mentally handicapped in 1841 in Abendberg. Jean Mark Gaspard Itard (1774-1838), a Parisian asylum doctor, tried to treat, Victor, the twelve year old feral³⁹⁵¹ 'Wild boy of Aveyron' in 1801, giving up in failure after six years. Edouard Seguin (1812-1880) opened his own school for the mentally retarded after training under Itard³⁹⁵². In British India, from the early 19th century, a policy of repatriation of the mentally ill back to England was used to disguise such vulnerability from the natives. Indian asylums were internally segregated according to race, class and sex. (Ernst, 1991)

It should be noted in passing that medical registration was established in 1858, the profession being disparate and unorganised before that date.



Treating the insane: rotating chair

³⁹⁴⁹ Friern Hospital from 1937 until it was closed in the 1990s.

³⁹⁵⁰ In England and Wales the number of lunatic asylums increased from nine in 1827 to almost 100 in 1920, the average number of inmates per asylum increasing from about 100 to nearly 1,000 in the same period.

³⁹⁵¹ The boy was probably autistic.

³⁹⁵² Later, in the USA, Seguin used peripheral stimulation in the hope of improving central nervous function, so-called 'sense training'.

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The superintendent of the Devon County Asylum, Sir John Charles Bucknill (1817-97), of Exeter, founded the *Asylum Journal* in 1853. The original Association of Medical Officers of Asylums and Hospitals for the Insane (AMOAHI) dates back to Dr Samuel Hitch. (Foster, 2004) He was resident superintendent of the Gloucestershire General Lunatic Asylum. Hitch wrote to colleagues in England, Ireland and Scotland in 1841 suggesting that an association be formed³⁹⁵³. The AMOAHI was replaced by the Medico-Psychological Association (MPA), the first president being W A F Browne, Commissioner of Lunacy for Scotland³⁹⁵⁴. The early MPA felt that it had to persist in its endeavours despite a hostile public perception of psychiatry. (Turner, 1991) In 1926 the MPA received a Royal Charter, becoming the RMPA. Its first president was John R Lord of Epsom³⁹⁵⁵.

The first words of *The Asylum Journal*³⁹⁵⁶ were: 'From the time when Pinel obtained the permission of Couthon to try the humane experiment of releasing from fetters some of the insane citizens chained to the dungeon walls of the *Bicêtre*³⁹⁵⁷, to the date when Conolly announced, that in the vast Asylum over which he presided, mechanical restraint in the treatment of the insane had been entirely abandoned and superseded by moral influence, a new school of special medicine has been gradually forming'. The *Journal of Mental Science* replaced the *Asylum Journal* and was itself replaced by the *British Journal of Psychiatry*³⁹⁵⁸ since 1963.

*The American Journal of Insanity (of Psychiatry)*³⁹⁵⁹ from 1921), the official journal of the Association of Medical Superintendents of American Institutions for the Insane, was founded in 1844.

The *Idiots Act* of 1886 made the simple distinction between greater (idiot) and lesser (imbecile) degrees of mental handicap. The first psychiatric ward attached to a general hospital was opened at Guy's Hospital in 1728. The first such unit to be opened in the USA was at the Albany Hospital in 1902. Ireland's first such unit was opened in Waterford³⁹⁶⁰ in 1967.

³⁹⁵³ The AMOAHI originally had chairmen (of meetings or sessions) – the first was Andrew Blake of Nottingham in 1841, but the most famous was John Conolly (1843 and 1851). Presidents were introduced in 1854 (A. J. Sutherland of London), and included Conolly (1858), Bucknill (1860), Joseph Lalor (Richmond Asylum, Dublin, 1861) and Henry Monro (Clapton).

³⁹⁵⁴ Other presidents included Maudsley of Hanwell (1871), James F. Duncan [took over from his father at Farnham House private asylum, Finglas – he was also vice-president of the College of Physicians] of Dublin (1875), J A Eames of Cork (1885), Conolly Norman of the Richmond Asylum (1894), Oscar T Woods of Cork (1901), W R Dawson of Dublin (1911), and Michael J Nolan of Downpatrick.

³⁹⁵⁵ Other holders included R R Leeper of St. Patrick's Hospital, Dublin, (1931) John Dunne (Grangeegorman, formerly the Richmond Asylum; 1955), William McCarten of Northern Ireland (1961), Desmond Curran (London, 1963), and Erwin Stengel (Sheffield, 1966). The first female president was A H A (Helen) Boyle (1939).



John Dunne

³⁹⁵⁶ November 15, 1853, price 6d.

³⁹⁵⁷ A former Carthusian monastery and part of the General Hospital of Paris from 1610.

³⁹⁵⁸ The editors of the latter were Eliot Slater, Edward H Hare, J L Crammer, Hugh Freeman, and Greg Wilkinson, the current editor being Peter Tyrer.

³⁹⁵⁹ Its first editor, until 1849, was Amariah Brigham (1798-1849), superintendent of the New York State Lunatic Asylum. The current, and twelfth, editor is Robert Freedman who took over from Nancy C. Andreasen of Iowa.



Amariah Brigham

³⁹⁶⁰ Tom Lynch (1922-2005; **see picture**) in charge: later Professor of Psychiatry, Royal College of Surgeons, Dublin.

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The *Lunacy Act* of 1890 maintained that a patient could be received into a mental institution if a relative, supported by two doctors, petitioned a justice. Other provisions entertained by the Act included an emergency order of short duration and special inquiries in the case of aristocrats. The same legislation allowed and for uncensored forwarding of certain letters written by inmates and for the relegation of restraint to the status of a specific medical intervention rather than something which any member of staff might apply.

Daniel McNaghten³⁹⁶¹ was found 'not guilty by reason of insanity' by the House of Lords in 1843³⁹⁶². McNaghten had wanted to kill the Prime Minister, but killed his private secretary, Edward Drummond³⁹⁶³ instead. The verdict was changed to 'guilty but insane' after Queen Victoria had been attacked³⁹⁶⁴. The modern version of the McNaghten Rules is as follows: (a) England - 'not guilty by reason of insanity' (changed back to this more recently); (b) Ireland (where the insanity defence is rarely used, probably because its acceptance means prolonged detention) was 'guilty but insane' (3/41 and 3/58 murder cases in 2002 and 2003 respectively) until the *Criminal Law (Insanity) Act* of 2006 when it became 'not guilty by reason of insanity'.

In 1879, Dr Abraham Cowles of the McLean Asylum, Massachusetts, started the first training school for attendants of the insane. Similar teaching was to commence in Scotland shortly after this. The MPA published *The Handbook for Attendants* in 1885, at the same time instituting an examination for doctors for a Certificate of Efficiency in Psychological Medicine, itself replaced by the Diploma in Psychological Medicine (DPM) in 1948.(Renvoize, 1991) The University of Edinburgh had already founded its Diploma in Psychiatry in 1912. The Membership of the Royal College of Psychiatrists (MRCPsych) examination was introduced in 1972.

During the 1890s Connolly Norman³⁹⁶⁵ of the Richmond Asylum³⁹⁶⁶ in Dublin insisted that attendants seeking promotion should pass an exam. Psychiatry became a compulsory part of undergraduate medical education in 1893.



St Brendan's Hospital, Dublin



³⁹⁶¹ An illegitimate wood turner from Glasgow. It is generally held that McNaghten was a paranoiac (delusional disorder) or, favoured by Rollin, (1996) had a schizophrenic disorder. McNaghten was placed in Bethlem Hospital but was eventually moved to Broadmoor Asylum, dying there on 3rd May 1865 aged 52 years.

³⁹⁶² A year later it became possible to transfer a sentenced prisoner to a criminal lunatic asylum (now 'special hospitals').

³⁹⁶³ 20 January 1843: shot in the back.

³⁹⁶⁴ Hit over the head by Lieutenant Robert Pate's walking stick and shot at by John Francis, William Bean and Edward Oxford.

³⁹⁶⁵ President RMPA and vice-president RCPI.(Walsh, 2009b)

³⁹⁶⁶ Ivor Browne's reaction when he saw this hospital (Grangegorman, St Brendan's) in 1959 (Browne, 2008, p. 67) was: 'There was a cacophony of sound and I felt as though I was lost in some kind of hell'.



Connolly Norman

The 1913 *Mental Deficiency Act* described mentally handicapped persons who from an early age showed strong 'vicious or criminal propensities' that were uninfluenced by punishment. A consequence of this Act was the locking away in asylums for long periods of retarded individuals who had outraged public morals, including girls who had become pregnant.

The case of Sir Roger Casement provides an example of how homosexuality was viewed publicly in the early part of the 20th century: following the 1916 rebellion in Ireland, Casement was sentenced to death. 'There were murmurs of a demand for reprieve. To silence these, the British government circulated passages, perhaps genuine, from Casement's diary, showing that he was homosexual. The demand was silenced. Casement was hanged.' (Taylor, 1981)

The theory of 'autointoxication' was popular early in the 20th century. For example, Henry Cotton of Trenton in the USA (d. 1933) pulled out patients' teeth and removed their colons in a vain attempt to cure mental disorder. Earlier, in the 1860s, Gustav Broun cauterised the clitoris and uterine cavity to reduce masturbation in women. (Porter, 2001b, p.105) Robert Battey made the removal of normal ovaries a popular procedure for women suffering from a variety of nervous disorders from the 1870s. (Porter, 2001b, p.228)

Masturbatory insanity (*onanism*³⁹⁶⁷)

Masturbation, a common human activity,³⁹⁶⁸ may be more overt among the mentally ill and may have become more obvious to medical practitioners when patients started to be admitted to asylums. Physicians who decried the myth were accused of supporting immorality. Denial of masturbation was often met with disbelief and guilty depressives often exaggerated their sins. Onan (*Genesis* 38.7-10) was punished for spilling his seed upon the ground, i.e. *coitus interruptus*. St Thomas Aquinas (1225-1274) stressed that sex was for marriage and only for procreative purposes. In 1708 the Dutch physician Herman Boerhaave (1668-1738) wrote that 'too lavish' a discharge of semen led to a wide variety of nervous problems that included convulsions, and dullness of the senses! S A D Tissot, a Swiss physician, published an influential book on the subject in 1758 which contained similar dire warnings. Benjamin Rush of Philadelphia published a book in 1812 in which he mentions masturbation as a cause of madness, impotence, poor sight, amnesia, and death! The effects of masturbation were considered to affect the health of offspring, perhaps an early attempt at epigenetic theorising! The Victorian gynaecologist Isaac Baker Brown FRCS (1812-1873: Fleming, 1960; Sheehan, 1985; Hare, 1998, ch. 8) practiced clitoridectomy³⁹⁶⁹ on women to prevent masturbation (a cause of insanity in his eyes) and as a cure for nymphomania! He was expelled from the Obstetrical Society in 1867 and his theories about masturbation were contradicted by Henry Maudsley, although Maudsley had earlier been an adherent of masturbatory insanity himself.³⁹⁷⁰ Kraepelin, writing in the 1890s, was categorical that masturbation never causes madness. Krafft-Ebing believed that homosexuality could stem from masturbation. Whilst belief in masturbatory insanity lingered on into the first half of the twentieth century it eventually gave way, in orthodox circles at least, to the view that, apart from religious considerations, the main consequence of masturbation *per se* was guilt.

A not dissimilar theory was that suppression of the flow of body fluids (e.g. nose bleeds, breast milk, and menstrual fluid) led to insanity.

³⁹⁶⁷ Onanism is a broader term than masturbatory insanity and includes penile withdrawal during intercourse.

³⁹⁶⁸ This was known to the great John Hunter who opined in 1786 that a rare phenomenon like lunacy could not be ascribed to a common practice like masturbation.

³⁹⁶⁹ Labia resection was to follow in due course. Males were sometimes subjected to infibulation (wring of the foreskin to prevent its movement)!

³⁹⁷⁰ Maudsley eventually came to the view that masturbation might be a symptom rather than a cause of madness. However, he believed that neurotic disorders could be caused by masturbation.

Forced sterilisation of the mentally ill began in Germany in 1936, with Hitler signing an order three years later which allowed for the gassing (carbon monoxide) of incurables, a situation which was opposed by a minority of psychiatrists (and others). (Meyer-Lindenberg, 1991; Burleigh, 2000, especially pages 29, 57, 126, 349, 379)

Perhaps the most famous case of post-influenzal depression was that of the American president, Woodrow Wilson, who was to suffer from it in 1919 during the peace conference in Paris (Churchill, 1933). In 1958, the South African, Joseph Wolpe (1915-97: later worked in Philadelphia), published *Psychotherapy by Reciprocal Inhibition*, and went on to develop the treatment known as systematic desensitisation. The Mowrers invented the bell and pad treatment for nocturnal enuresis in 1938.



Joseph Wolpe

The 1930 *Mental Treatment Act* allowed for three admission categories, one of which recognised the person who might be admitted voluntarily (and might discharge himself by giving three days notice). This was later replaced by the 1959 Mental Health Act, which removed judicial involvement in civil admissions and replaced the term 'voluntary' with 'informal'. The earlier association of asylums with only involuntary care may have branded them as places one sent people to as a final resort. (Porter 2001b) The current legislation is the *Mental Health Act* 1983 (England & Wales) although this is likely to change soon. The English *Homicide Act* of 1957, reflecting a long tradition in Scotland (Walker, 1968), permitted a defence of diminished responsibility to a charge of murder. If successful, the conviction is of manslaughter, allowing the judge wider choice of disposal. This reduced the use of the 'not guilty by reason of insanity' plea (*vide supra*). The *Irish Criminal Law (Insanity) Act* 2006 permits a defence of diminished responsibility.

An out-patient clinic³⁹⁷¹ was opened at St Thomas' Hospital, London, by Dr T Rayner in 1889, one year after John Chapin had done the same at Pennsylvania General Hospital. (Shorter, 1997) By 1936 the number of such clinics in England and Wales stood at 166. Dr J Carse of Graylingwell Hospital, Chichester, started the 'Worthing Experiment' in 1957: a day hospital³⁹⁷², out-patient clinic, and domiciliary service reduced admissions from Worthing by 59%. (Carse et al, 1958) The first occupational therapy school was opened at Dorset House, Bristol by Dr Elizabeth Casson in 1930, and the Association of Occupational Therapists was formed six years later.

The launch of the National Health Service in 1948 initiated the difficult process of integrating mental health services with the general body of medical services, thus, at least *de jure*, freeing them from 'the taint of the Poor Law and lunacy code'. (Webster, 1991) The National Institute of Mental Health (NIMH), part of the federal National Institutes of Health of the US Department of Health and Human Services, was founded in 1946 with responsibility for research on causes, treatment and prevention of mental illness.

The 1950s saw the start of the 'open door movement'. In fact open doors were to be found in Fife and Kinross Asylum in the 1870s under Dr John Batty Tuke, no relation of the York Tukes. By 1956 there were seven hospitals in England with no locked wards, after a renewal of locking-up during the staff-shortages of World War II. In 1963, John F Kennedy gave the only presidential message to Congress on mental illness and intellectual disability, leading to the establishment of Community Mental Health Centres (CMHCs). These were poorly funded and catered for the less mentally disturbed. Jimmy Carter established a President's Commission on Mental Health in 1977 which increased funding for community psychiatry³⁹⁷³. However, Ronnie Reagan repealed this legislation in 1981, before it could be implemented. More recently, Americans have experienced managed care and privatisation. (Duckworth & Borus, 1999)

³⁹⁷¹ Gk., *kline*, a bed.

³⁹⁷² Joshua Bierer opened the Marlborough Day Hospital, in a house that once belonged to Charles Darwin's associate Thomas Huxley, around the same time. A night hospital was situated in the stables, at first operating weeknights but later also at weekends. (Browne, 2008, p. 70)

³⁹⁷³ Via an Act of 1980.

'Total institution' (Goffman, 1961)³⁹⁷⁴

Described the worst aspects of asylum life³⁹⁷⁵

Inmates did everything in the one spot

Everything was regulated

Absence of social roles found in general life

Nurses decided on medical visitation and 'carried' the hospital culture

Progressive loss of patient autonomy

The British *Criminal Procedure (Insanity and Unfitness to Plead) Act* of 1991 abolished automatic detention for an indefinite period for defendants found unfit to plead, so ending what professionals had long viewed as an injustice. People found unfit to plead before this legislation could be detained in hospital without any finding as to guilt or innocence.

Seebohm Report (UK)

In 1974 social services were reorganised

Provision of social work services to hospitals became a local authority responsibility

Specialist psychiatric social workers³⁹⁷⁶ (PSWs) were absorbed into the pool of 'generic' social workers

The Swede Magnus Huss introduced the term alcoholism³⁹⁷⁷ in 1851, although Thomas Trotter, a former Navy doctor, had described the 'habit of drunkenness' as a 'disease of the mind' in his 1804³⁹⁷⁸. In 1915, Lloyd George introduced restrictions on drinking hours to promote sobriety in the workforce which helped to reduce alcohol consumption for a decade. During *Prohibition* in America the number of deaths from hepatic cirrhosis fell significantly, but organised crime became a major problem. Alcoholics Anonymous (AA), taking its name from a book title, was founded in Akron, Ohio in 1935 by two alcoholics³⁹⁷⁹. Gamblers Anonymous (GA) was founded in Los Angeles in 1957.

The first report of Mad Hatter's disease (mercurialism) came from New Jersey in 1860, five years after Lewis Carroll's *Alice in Wonderland*. (O'Carroll et al, 1995) It is said that Carroll³⁹⁸⁰ suffered from temporal lobe epilepsy which might account for his characters passing through mirrors or changing in size. The professional history of anorexia nervosa (AN) goes back at least to 1694 and Richard Morton's 'nervous consumption', distinguishing such cases from tuberculous *phthisis*; and Lasegue coined the term 'hysterical anorexia' in the same year as William Gull (1874) published his paper containing the modern name of the condition in its title, although Gull had discussed the problem at Oxford and in the *Lancet* six years previously. (Gull, 1868) Lasegue of Paris is credited with the simultaneous description of AN, calling it *anorexie hysterique*. Between 1914 and 1949 it was confused with Simmond's disease, AN patients being treated with pituitary extract. Gerard Russell (1979) described his 'ominous variant' of AN, bulimia nervosa, (BN) twenty years before binge eating disorder was described by Stunkard in 1959. (Stunkard, 1959) although the latter may overlap considerably with non-purging BN. (Garfinkel, 1999) In 1993, using loss of 'disability adjusted life years' or DALYs, the World Bank concluded that psychiatric illness was second only to cardiovascular disease worldwide in economic terms. (World Bank, 1993) Subspecialty status for the psychiatry of old age was granted by the Royal College of Psychiatrists in 1989. The two major classification systems used in psychiatry date from 1948 (*International Classification of Diseases* of the World Health Organization: ICD-6) and 1952 (*Diagnostic and Statistical Manual* of the

³⁹⁷⁴ The sociologist Andrew Scull (2010), in a very negative overview of psychiatry, suggests that modern medicines had only a minor role in the closure of large Victorian institutions and that the main reasons for such changes were to save money. Scull also warns us to beware of pharmaceutical industry sponsorship (e.g. non-publication of 'inconvenient data'). It was Scull (1979) who described asylums as 'museums of madness'.

³⁹⁷⁵ Rare disasters have occurred in closed asylums, such as the deaths of many inmates from fire. (Rollin, 1989)

³⁹⁷⁶ The 'approved' social worker, with a statutory role in committal procedures, was a child of the Mental Health Act 1983.

³⁹⁷⁷ The word alcohol comes from the Arabic for essence, *Al kihl*.

³⁹⁷⁸ In his classic *Essay Medical Philosophical and Chemical on Drunkenness*.

³⁹⁷⁹ 'Bill W', (1895-1971) a New York stockbroker, and 'Dr Bob S', (1879-1950) a surgeon from Akron. The first meeting in Europe was held in the Country Shop Restaurant, St Stephen's Green in Dublin on November 18, 1946.

³⁹⁸⁰ His real name was Charles Lutwidge Dodgson (1832-1898).

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APA: DSM-I³⁹⁸¹). The current forms, which are less divergent in content than their predecessors, are ICD-10 (1992) and DSM-IV (1994) respectively.

Ireland

A number of terms were commonly used in Ireland during the seventh and eight centuries (see box), the time of the *Brehon Laws*. *Brehon* refers to justices who travelled early Christian Ireland. Under these Laws, the *conn* or guardian of an insane perpetrator was often held responsible for his actions.

Some old Irish terms

Cailleach - old hag who was able to transfer mental illness from one person to another

Madman's wisp - pre-Christian ball of straw or grass thrown in someone's face by a Druid, unfortunate victim going mad

Dásachtach - potentially violent manic person ('battle madness' of the Celts)

Mer - a less dangerous deranged person

Drúth - intellectually disabled person or a professional clown who mimics a mad person

Glen-na-Galt (Valley of the Madman) - possibly on the Dingle Peninsula in County Kerry, although there were many such valleys; mentally ill people who drank there from a holy well known as *Tobair-na-Gealt* were often said to recover their senses

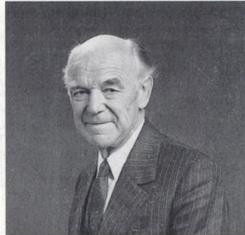
St Dymphna, an Irish princess, fled to Belgium from her incestuous father, only to be murdered by him at Gheel, which later developed into a famous home-care centre for the mentally ill and retarded.



Following the death in 1745 of Jonathan Swift, Dean of St Patrick's, and using money that he left in his will, St. Patrick's Hospital, Dublin 8, was founded a year later³⁹⁸².

St Patrick's Hospital, Dublin

During the early 19th century, 'mad' peasants were sometimes kept in a hole in the cabin floor with a crib over the opening.(Shorter, 1997) Many Irish lunatics were incarcerated in gaols and houses of industry.(McClelland, 1988) In 1773, the House of Industry was opened at North Brunswick Street³⁹⁸³ for the relief of the poor of Dublin City³⁹⁸⁴. The *Prisons Act* of 1787 allowed for the establishment of lunatic wards in Houses of Industry.



Norman Moore (1911-1996)

³⁹⁸¹ DSM-I was a response to the Veteran's Administration post-war diagnostic handbook.

³⁹⁸² Its first inmates were received some years later. The St Edmundsbury Estate (Lucan) was added in 1898.(Malcolm, 1989)

³⁹⁸³ Under 1772 legislation.

³⁹⁸⁴ Other similar houses were opened in Clonmel, Cork, Waterford, and Limerick.

Money became available to start building the Richmond Asylum in 1810.(O'Shea & Falvey, 1996) This Asylum remained as the 'Lower House' (of St. Brendan's Hospital) until it was closed in 1989, having had its first admission in 1814. The first Irish asylum for the mentally handicapped was opened in Dublin in 1869: the Stewart Institution for Imbecile Children.

1817 saw the establishment of a national asylum system for Ireland, far ahead of other countries³⁹⁸⁵. Also, Irish admission rates increased faster than in England. Now, as then, single males are the most commonly admitted group, and it has been speculated that 19th century inheritance and emigration practices (young women leaving, second or other sons being admitted for violence rather than illness) favoured this outcome. Families were the main initiators of admission, not doctors or politicians.(Malcolm, 1999) Immigration was thought to have left lunatics and idiots behind without healthy people to look after them. Also, returned emigrants may have become mentally ill as a result of their experiences. Society gradually became less tolerant of the insane and overcame any reluctance to incarcerating them. Increased longevity may have made the mentally ill more obvious in society.(Walsh & Daly, 2004) Also, asylums gave jobs to the local community (often over many generations), which may have played a part in resistance to their closure. Lastly, there was the 'pressing need to remove lunatics from prisons and workhouses'.(Stevenson, 2004, p. 1505)



Connaught Lunatic Asylum (St Brigid's) opened 1833

A French Law of 1838 'played a critical, if indirect, role in' establishing 'a collective professional identity' among French psychiatrists/alienists.(Goldstein, 2004) It mandated the building of a national network of asylums staffed by doctors appointed by the Minister of the Interior³⁹⁸⁶. French physicians could not understand the absence of full-time doctors in British (or Irish) asylums.(Goldstein, 2004; see Walsh & Daly, 2004, p. 85)

1846 saw the opening of an Office of Lunacy in Dublin Castle. Dr Francis White was appointed Inspector of Lunatics, joined some time afterwards by Dr John Nugent³⁹⁸⁷.

In 1884 there were 45 asylums in all of Ireland³⁹⁸⁸. According to a Select Committee of 1814/15, corpses were simply left in some rooms where there were patients, and two or three patients were in the one single bed. In 1861, Ireland officially had 7,065 lunatics and 7,033 idiots, both categories being divided equally between the sexes. On 31.12.1883 the total number of registered lunatics in Ireland amounted to 14,088. These were kept in the various asylums and in the 163 poor houses. (Miles, 1988) An 1867 Act³⁹⁸⁹ authorised magistrates to commit dangerous lunatics and idiots to mental asylums, shortly becoming the main instrument by which any mentally disordered person could be compulsorily detained in an asylum,(Reynolds, 1992) being criticised by Norman (1886) as a social policing policy, and leading inevitably to gross overcrowding in district asylums. McClelland (1988) posits two chief reasons for the increase in Irish asylum provision³⁹⁹⁰: recognition of the numerical frequency of the problem in the community and the prevailing poverty that meant that relatives could not afford home-based care.(see Walsh, 2008) By World War I, Ireland had a resident insane population of 0.5% of total population³⁹⁹¹.(Bartlett & Wright, 1999) Overcrowding was a major obstacle to any hopes of rehabilitating inmates.(Andrews, 2004, p. 315)

³⁹⁸⁵ 1838: France & Switzerland; 1845: England & Wales; 1848: Norway; 1850: Belgium; 1857: Scotland.

³⁹⁸⁶ It also inspired the founding of a psychiatric journal (*Annales médico-psychologiques*) in 1843.

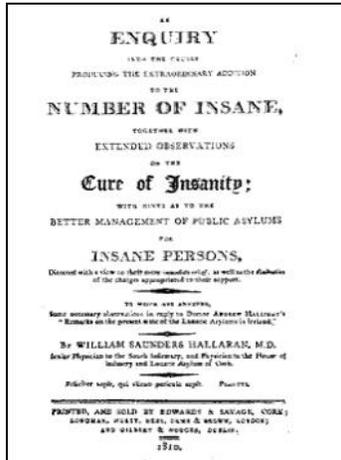
³⁹⁸⁷ Nugent had been physician to Daniel O'Connell.

³⁹⁸⁸ 22 district, 22 private, and one criminal.

³⁹⁸⁹ 30 + 31 Vic. c. 118

³⁹⁹⁰ The total number of registered insane in 1890 was 16,159 (8,115 males, 8,044 females): 11,180 in district (public) asylums; 4,165 in poor-houses; 637 in private asylums; 176 criminally insane; and one (!) in gaol.(Anonymous, 1891)

³⁹⁹¹ England and Wales had a figure of 0.37% by 1909; and Scotland had similar rates of residence.



Cover of Ireland's first textbook of psychiatry

In 1810, William Saunders Hallaran³⁹⁹² (1765-1825) of Cork, viewed as one of the founders of Irish psychiatry, published the first edition of *An Enquiry into the Causes producing the Extraordinary Addition to the Number of Insane together with Extended Observations on the Cure of Insanity with Hints as to the Better Management of Public Asylums for Insane Persons*³⁹⁹³, anticipating therein much of the basic ideas of moral treatment, although he was the 'inventor'³⁹⁹⁴ of a rapidly revolving chair for the treatment of insanity. (Williamson, 1970) He also advocated art therapy and early discharge. Kelly (2010), while discussing the modern early intervention in psychosis debate, suggested that Hallaran advocated early, frequent and prolonged use of emetics in psychotic patients and quoted Hallaran as insisting that patients became more subdued as a result of this intervention!

The Irish Division of the MPA was formed in 1872, but many Irish alienists were members before this time. The Resident Medical Superintendent (RMS) became the undisputed authority, albeit answerable to a Board of Governors, in 1862. In 1892, the post of visiting physician was abolished, removing a former source of power struggles with RMSs. The first female member of the MPA, Eleanora Fleury, a clinical assistant at Dublin's Richmond Asylum, was nominated by its president, Connolly Norman (1853-1908), in 1894.³⁹⁹⁵ Walsh (1992a) hailed Norman as 'probably the most far-sighted and perceptive of all Irish psychiatrists'.

Asylums become known as psychiatric hospitals following the 1925 *Local Government Act*. In 1947 the law for the first time allowed for the admission of voluntary patients to Irish psychiatric hospitals under the *Mental Treatment Act* of 1945. (Robins, 1986) A *Health (Mental Services) Act* of 1981 never came into effect and the *Mental Health Act 2001* is the current legislation³⁹⁹⁶. The last Act is a product of concern over civil liberties. (Mills, 2001)

The Brothers of St John of God arrived in Ireland in 1879 and, starting from Clonmel, offered services for the mentally ill and handicapped throughout the country. The headquarters is at Stillorgan.

In recent years the high walls around institutions were torn down, community-based services were developed to a variable degree, psychiatric in-patient and outpatient services were developed at general hospitals. (Rose, 2001) Sectorisation³⁹⁹⁷ was pressed by the Government. Ireland has similar problems to the UK when funding its community-based endeavours. (O'Shea, 1998b)

³⁹⁹² He is known as the 'first Irish psychiatrist'. 1799 saw the opening of a private Cork asylum, Citadella, which he opened. He was a former pupil of William Cullen of Edinburgh. Alexander Jackson (1767-1848) was the first physician to the Richmond Asylum, Dublin, from 1815; started private asylum, *Farnham*, at Finglas north of Dublin.

³⁹⁹³ The 1818 edition was titled *Practical Observations and the Causes and Cure of Insanity*. Both editions were published by Edwards and Savage of Cork.

³⁹⁹⁴ In fact he was inspired by Dr Edward Mason Cox (1763-1818) of Scotland who invented his own suspended chair. (Kelly, 2008)

³⁹⁹⁵ Dominic Corrigan, the famous Dublin physician, was abhorred!

³⁹⁹⁶ The Government there seemed set on increasing social control through psychiatry according to Moncrieff. (2003). The 2001 Act has considerable resource implications and caused some unease when it was introduced. (Clinton, 2002)

³⁹⁹⁷ A sector is a unit of 25-30,000 population, and run by a consultant psychiatrist.

Involuntary admission rates remained high compared to England & Wales and Italy.(Daly & Walsh, 2000) Italian legislation in 1978 forced a movement out of mental hospitals and into the community and acute in-patient units, but ‘many in-patient facilities [show] significant limitations in terms of architectural and logistic characteristics’.(De Girolamo et al, 2007)

Pope John XXII³⁹⁹⁸ cut attempted suicides off from the sacraments until they had repented. The Brahmins of India practiced suttee where widows fell on the pyre of her late husband³⁹⁹⁹. The Code Napoleon decriminalised suicide in France in 1810. An 1823 Act in Britain abolished the practice of burying suicides and murderers in unconsecrated ground.(Arnold, 2007, p. 187) Under the provisions of the *Suicide Act 1991*, Ireland caught up with Britain (*Suicide Act 1961*) and suicide ceased to be an illegal act, although anyone who counsels or procures the completed or attempted suicide of another shall be liable to conviction or indictment to imprisonment for a term not exceeding ten years (14 years in England).

Examples of mass suicides are Masada in Israel where Jews died on top of a mountain in order to avoid capture by the besieging Romans in AD 73, Saipan in 1944 where Japanese civilians jumped off Banzai Cliff to evade US soldiers, and Jonestown, Guyana in 1978 where 918 Americans, including 274 children, led by Jim Jones, founder and leader of the ‘Peoples Temple’ committed suicide.



Anthony Clare (1942-2007)

Finally, in 2002, the then Irish Division of the Royal College of Psychiatrists spawned separate Sections for the Republic and for Northern Ireland. This move, following hard on the heels of the inauguration of the Irish Psychiatric Association, was in response to the necessity of having a separate organisation to deal with issues directly relating to the Republic. In 2002 the Republic Section of the Irish Division became the Irish College of Psychiatrists (*Coláiste Síciatraithe na hÉireann*). Political changes in Britain spurred moves to an autonomous Irish college, The College of Psychiatry of Ireland⁴⁰⁰⁰ (*Coláiste Síciatrachta na hÉireann*) which came into being on January 1, 2009.(Walsh, 2009a)

Psychiatric Nursing

During the 18th century, Dr Nathaniel Cotton of St Albans insisted on high quality environment and nursing, emphasising calmness, relaxation, civility, and humanity. Dr William Battie, in the same period, noted that staff was ignorant, disinterested, and transient. William Tuke founded the York Retreat in 1796. He hoped its quietude would promote mental healing. His first attendant, George Jepson, employed a humanitarian approach, with Bible readings, discussions on healthy living, and seaside outings. Dr Thomas Story Kirbride of the Pennsylvania Hospital commenced formal instruction in 1843. In 1851, Dr W A F Browne, of the Crichton Royal Hospital, Dumfries, in Scotland, started an organised course for attendants. The world’s first School of Nursing, at McLean Hospital, was opened in 1879 (some authors date it from 1882), another being opened at Buffalo State Hospital in 1883.

In 1885, the MPA introduced *The Handbook for the Instruction of Attendants on the Insane*, renamed *The Handbook for Mental Nurses* in 1923. The first national training scheme for mental nurses/attendants started in 1891, successful candidates receiving a Certificate of Proficiency in Nursing the Insane. Males were not accepted as members of the Royal College of Nursing⁴⁰⁰¹ until 1960.

The Asylum Workers’ Association was formed in 1896 to improve the low status of asylum workers. The Asylum Workers’ Union started in 1910, followed eight years later by industrial action. Working

³⁹⁹⁸ Pope from 1316 to 1324.

³⁹⁹⁹ However, Sanskrit had a negative view of suicide.

⁴⁰⁰⁰ The logo consists of a snake and three candles of illumination with Wisdom (*Eagna, Logos*), Learning (*Léam, Sophia*), and Compassion (*Chomhbhá, Pathos*). The College incorporates the Irish Psychiatric Training Committee, the Irish College of Psychiatrists, and the Irish Psychiatric Association. The first president was Justin Brophy.(Vize, 2009)

⁴⁰⁰¹ It was known as the Royal British Nursing Association pre 1919.

conditions were very poor. According to Nolan (1991), the introduction of courses and certificates did little to improve the lot of attendants, and may have helped to prompt the formation of unions in protest at poor working conditions.

Lena Peat of Warlingham Park Hospital, Surrey, with the backing of the hospital's medical superintendent T P Rees, became the first community psychiatric nurse⁴⁰⁰² in Britain in 1954. A nursing post created to look after the chronically ill in the community has become increasingly aligned with primary care and, arguably, the less severely ill. 1963 saw the introduction of the first psychiatric nursing journals⁴⁰⁰³ in Britain.

Project 2000 in England removed nurse education from hospitals (apprenticeship model) and into universities (theoretical model). An 18-month foundation programme⁴⁰⁰⁴ was followed by a further 18-month period of largely theoretical specialisation. Clinical experience is given much less emphasis than in the past. Gournay (2001) suggested that an anti-psychiatry ambience may be alive and well in 'many university departments of nursing' and he bemoaned the loss of those elements of apprenticeship 'which are so valuable to the training of nurses'. Similar trends have appeared in Ireland in recent years, compounded by a serious lack of entrants to nurse training. Apart from pay and career issues, the present author does not believe that matters are helped by the closure of (cheap) nurses' homes and the (prohibitive) 'points system' employed by universities to award places in nursing departments. There is also the danger that newly qualified nurses will not wish to undertake many traditional nursing duties⁴⁰⁰⁵.

Child Psychiatry

Elementary school attendance was made compulsory in Britain in 1880, highlighting a 'surprisingly high proportion' of poor copers due to learning (syn. intellectual) disability, emotional and behavioural problems. (Wardle, 1991) The first British school for mentally subnormal children was Whites School for Imbeciles, opened at Bath in 1846. The first asylum in Britain dedicated to this group was The Asylum for Idiots, Park House, Highgate in London, established two years later.

In 1896, Cattell and Witmer started a multidisciplinary clinic in the US. In 1904/5, Alfred Binet and Simon published their intelligence test, introducing the concept of mental age based on knowledge of average intelligence level at a particular age; Lewis Terman of Stanford University devised the Stanford-Binet Test in 1916; and David Wechsler of New York designed his Adult Intelligence Test (WAIS) in 1939. Starke Hathaway, a psychologist, and J Charnley McKinley, a psychiatrist produced the MMPI, the most commonly used test of personality, in 1937.

Meyer introduced a psychiatric social worker at Manhattan Hospital in 1906. Three years later, Cyril Burt became the first educational psychologist to London County Council (LCC). In the US, the Smith College opened its school of social work in 1918. The Tavistock Clinic had its first child patient in 1920 and by 1923 there were 15 demonstration child-guidance clinics (CGCs) in America. Mapother encouraged child clinics at the Maudsley during the early 1920s, and an East London CGC was started in 1927. Lowenfeld started a play-therapy group during the following year. Training and demonstrations were organised at a London CGC which had been opened by Moodie in 1929. Klopp established an in-patient unit in the US one year later (the Maudsley unit did not open until 1947), and a neuropsychiatric clinic started in America in 1931. Birmingham CGC opened in 1932⁴⁰⁰⁶. Three more years saw the publication of Kanner's textbook of child psychiatry.

H Bickel, J Gerrard and E M Hickmans reported in 1953 that removing phenylalanine from the diet of children with phenylketonuria prevented further intellectual deterioration.

Some historical aspects of drug treatments in psychiatry

Perhaps the oldest drug is mead⁴⁰⁰⁷, fermented from honey.

The bromides, useful in epilepsy, were originally used to reduce sexual urges⁴⁰⁰⁸. Chloral hydrate⁴⁰⁰⁹ was synthesised by Justus Von Liebig in 1832 and introduced by Liebreich as a hypnotic in 1869.

⁴⁰⁰² CPN, more recently dubbed 'community mental health nurse' or CMHN.

⁴⁰⁰³ *Perspectives in Psychiatric Care* and the *Journal of Psychiatric Nursing and Mental Health Services*.

⁴⁰⁰⁴ Sometimes it had little psychiatric content.

⁴⁰⁰⁵ A fear shared by many experienced nurses.

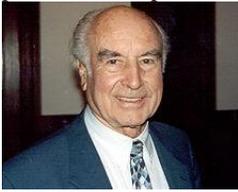
⁴⁰⁰⁶ Other early innovations were an adolescent unit at Epsom in 1947, and, in the next year, child psychiatrists officially became involved in assessing maladjusted children.

⁴⁰⁰⁷ This alcoholic drink dates to circa 8000 BC. (Belzung et al, 2002)

⁴⁰⁰⁸ And hence 'masturbation insanity'!

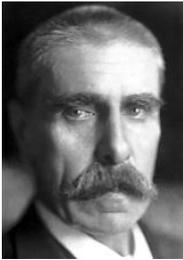
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Paraldehyde⁴⁰¹⁰, formerly used as a hypnotic and for the treatment of prolonged convulsions, was synthesised by Wiedenbusch in 1829 and was introduced to medicine by Covello in 1882. Morphine⁴⁰¹¹ was isolated in 1803 by W F A Setürner of Paderborn. Bayer had introduced the newly developed heroin in 1898. Hyoscine was synthesised by Schmidt in 1888. Barbituric acid, (malonylurea) prepared by Von Baeyer in the 1860s and named after St Barbara, gave rise to a new group of synthetic psychotropics, the barbiturates⁴⁰¹². Amphetamine was developed in 1927 by Gordon Alles as a substitute for ephedrine in the treatment of asthma, but never achieved the hoped-for popularity in the treatment of depression, except in the USA where the amphetamines are employed in attention-deficit disorder and refractory depression⁴⁰¹³. Opiates and scopolamine were also used for a time in psychiatry, to quieten disturbed patients. In 1943, Hoffmann⁴⁰¹⁴ took lysergic acid diethylamide (LSD) himself and confirmed the psychic phenomena reported by volunteers.



Albert Hoffman (1906-2008)

Salvarsan, an arsenical, the 'Magic Bullet', was introduced by Paul Ehrlich in 1910 for the treatment of general paralysis of the insane⁴⁰¹⁵. In 1917 Wagner Von Jauregg of Vienna used malarial therapy⁴⁰¹⁶ for GPI.



Julius Wagner-Jauregg (1857-1940)

Again in Vienna, Manfred Sakel used injections of insulin in 1927 to induce hypoglycaemic coma⁴⁰¹⁷. 'Modified' insulin treatment followed - drowsiness short of coma. The extra care given by enthusiastic staff

⁴⁰⁰⁹ Now chloral betaine, a pro-drug that must be metabolised to trichlorethanol to produce its hypnotic effect. It is still used as triclofos. Chloral hydrate with alcohol (Mickey Finn) was used to knock out sailors who were being shanghaied. Trichlorethanol slows ethanol metabolism and the latter quickens chloral hydrate's conversion to trichlorethanol.

⁴⁰¹⁰ Now obsolete. It had to be administered in a glass syringe and could cause metabolic acidosis, sterile abscesses, nerve damage and sloughing of skin. Paraldehyde is not as safe in people with liver dysfunction as once thought and is mostly metabolised by the liver with only a small proportion being excreted via the lungs.

⁴⁰¹¹ Gk., *Morpheus*, god of dreams.

⁴⁰¹² Phenobarbitone was introduced in 1912. The toxicity and dependence associated with barbiturates have severely restricted their use. Suphonal, a powerful tranquilliser derived from acetone in 1886, is no longer in use. Diphenylhydantoin (phenytoin), a much less toxic agent than phenobarbitone, was discovered by Merritt and Putnam (1958) from the examination of a series of phenyl compounds. They reported their findings in San Francisco in 1938.

⁴⁰¹³ They are also dependence producing, may induce a paranoid psychosis, and can lead to severe depression.

⁴⁰¹⁴ A chemist at Sandoz Laboratories. Patients given LSD during the late 1950s and early 1960s are now seeking legal compensation. (Dyer, 1995) Medical uses of LSD included treatment for everything from homosexuality to alcoholism, and the induction of 'model psychoses'.

⁴⁰¹⁵ *Dementia paralytica* or GPI.

⁴⁰¹⁶ John Dunne brought this therapy to Ireland.

⁴⁰¹⁷ It was claimed to be beneficial in schizophrenia, although Sakel's original curiosity was aroused by noted similarities between hyperthyroidism and the opiate withdrawal syndrome – he used insulin as a 'thyroid antagonist' to treat this abstinence state before turning to treat schizophrenic patients.

may have offered non-specific benefits. Insulin therapy fell into disuse because coma induced by barbiturates gave equally good results⁴⁰¹⁸.(Ackner et al, 1957)



Manfred Sakel

Giuseppe Epifanio of Turin had employed barbiturate narcosis in the treatment of severe mental disorder as early as 1917.

Just before the time of Galen, Scribonius Largus⁴⁰¹⁹ applied electric eels to the forehead for headache.(Krzyzowski, 1989; Finger, 2000) In 1785, W. Oliver reported giving camphor⁴⁰²⁰ to a patient with mania. After a generalised convulsion the patient recovered temporarily (Oliver, 1785).

Ladislav Von Meduna believed, erroneously, that schizophrenia and epilepsy could not co-exist. After using camphor oil to induce convulsions he switched to Cardiazol (soluble solution of synthetic camphor⁴⁰²¹) in 1934. Other agents were eventually added to the list of epileptogens, such as picrotoxin.

Cerletti and Bini introduced electroconvulsive therapy (ECT)⁴⁰²² after some preliminary tests in Roman slaughterhouses. This was later modified by the use of a general anaesthetic and a muscle relaxant.

Wilder Penfield, a Canadian neurosurgeon, removed a scar on the brain in 1927. He then worked with Otrid Foerster in Breslau on the removal of atrophic epileptiform lesions, leading to an enormous number of operations on epileptics in later years. Penfield discovered that some epileptics showed bilateral and symmetrical EEG patterns during seizures which led to his theory that seizures arose from the central brainstem, i.e. centrencephalic epilepsy. Egas Moniz, the originator of cerebral angiography, founded modern psychosurgery by cutting pathways in the prefrontal areas in 1935. In 1945 Freeman introduced a more extensive operation in America. The German neuropsychiatrist Hans Berger (1873-1941) developed electroencephalography (EEG) in 1929. The Gibbs (Frederic and Erna) and William Lennox recorded the EEG in epilepsies in 1935.

Antipsychotic drugs

Reserpine (a *Rauwolfia*⁴⁰²³ alkaloid) - used for many of purposes, including the treatment of psychosis

Methylene blue - has a phenothiazine nucleus and was used briefly as an antipsychotic

Phenothiazine - synthesised by August Bernthsen in 1883; first used as an antihelminthic in 1934

Chlorpromazine - synthesised by Charpentier in 1950 at Rhone-Poulenc laboratories⁴⁰²⁴

Laborit⁴⁰²⁵ used chlorpromazine to induce artificial hibernation during operations, noticing a certain 'detachment' in his patients

⁴⁰¹⁸ The analyst Smith Ely Jelliffe believed insulin therapy to work by 'withdrawing the libido from the outside world and fusing it with the death impulse for the maintenance of the narcissistic ego'!(Shorter, 1997)

⁴⁰¹⁹ *Compositionis Medicamentorum*, 43-48 AD.

⁴⁰²⁰ Camphor was given IM in oil at first, nausea and vomiting were common, and it was impossible to forecast the time or duration of the fit. Weickhardt also used camphor to induce fits in 1798.

⁴⁰²¹ Pentylene tetrazol (Cardiazol in Europe, Metrazol in US) given IV; anxiety before fit was common and painful thrombosis could follow.

⁴⁰²² Electricity became popular among asylum doctors in the second half of the 19th century because of major developments in electrical science and because of its scientific appeal. They did not seek convulsions, the latter being considered undesirable. Electrification of the skin was the therapeutic aim at first, but later on the electrodes were applied to the head (Beveridge and Renvoize, 1988). Robert Remak, in his *galvanotherapie* of 1858, recommended the use of the constant current in abnormal brain conditions associated with mental disorder.

Emil du Bois-Reymond (1818-1896) of Berlin, a student of Johannes Peter Müller and a friend of Hermann von Helmholtz, is credited with the discovery of the nerve action potential.

⁴⁰²³ Leonhard Rauwolfia, a Bavarian physician, travelled in the Middle East during the 1570s and was the first European to describe the preparation and drinking of coffee.(Savage-Smith, 2001, p. 52)

⁴⁰²⁴ During attempts to find more suitable phenothiazine derivatives than promethazine (Phenergan).

⁴⁰²⁵ French surgeon Henri Laborit (1914-95).

Jean Delay⁴⁰²⁶ (1907-87) and Pierre Deniker (d. 1998), Parisian psychiatrists, introduced chlorpromazine to psychiatry in 1952 as a tranquilliser (Moussaoui, 2002) and described the neuroleptic⁴⁰²⁷ malignant syndrome in 1968

Montreal psychiatrist Heinz Lehmann (1911-99) introduced chlorpromazine in North America
Other early antipsychotic drugs: the butyrophenones haloperidol⁴⁰²⁸ (1959), benperidol (1965), and droperidol (1963), the thioxanthenes clopenthixol (1959) and flupenthixol (1963), and the depot neuroleptics fluphenazine enanthate (1963) and fluspiriline (1968)

Clozapine⁴⁰²⁹ ('first atypical neuroleptic') synthesised in 1958 by Hünziker and co-workers; found effective in chronic schizophrenia four years later, although its development was delayed by reports of granulocytopenia in 1975 (McKenna & Bailey, 1993)

Risperidone (another atypical antipsychotic) available to clinicians from 1993

In 1963, the Swedes Carlsson and Linqvist noting elevations of homovanillic acid in cerebrospinal fluid postulated that the then available neuroleptics blocked dopamine receptors. The American *Omnibus Reconciliation Act* of 1987 was meant to tackle the perceived overuse of antipsychotic drugs in nursing homes, a problem that persists closer to home.(Anonymous, 2003)

Alfred Garrod (1859) used lithium⁴⁰³⁰ to treat gout. There were even instances of its use in the 19th century for 'gouty mania'.(Schou, 1992) In the 1940s, a number of patients died when lithium chloride was used as a salt substitute in patients with heart disease. In 1949, after work involving the injection of the urine of manic patients into guinea pigs⁴⁰³¹, John Cade of Australia reported excellent results with lithium in the treatment of mania.



John Cade 1912-1980

The anticonvulsants, especially carbamazepine and sodium valproate have encroached on the prophylactic hegemony heretofore enjoyed by lithium for episodic mental illnesses; their psychotropic actions were described in Japan by Okuma and associates in 1973 and in France by Lambert in 1965, respectively. Roland Kuhn reported on the antidepressant effects of imipramine⁴⁰³², an iminodibenzyl derivative, at Zurich in 1957.(Kuhn, 1958) This was followed by amitriptyline. The first monoamine oxidase inhibitor (MAOI) antidepressant, iproniazid, was discovered during a search for agents active against Koch's bacillus. This hydrazine derivative was developed from a fuel used to propel Nazi V2 rockets!(LeFanu, 1999) Iproniazid is chemically very similar to isoniazid. Barry Blackwell first reported the hypertensive crisis associated with tyramine-MAOI interactions in 1963. An MRC trial in Britain made the MAOIs appear ineffective because of the use of excessively low doses.(Healy, 1999) Modern serotonin reuptake inhibitors or SSRIs include fluvoxamine, introduced in 1987, followed by fluoxetine, sertraline, and paroxetine, with citalopram and then escitalopram following later. Some modern psychotropics were in clinical use before their unacceptable toxicity led to their withdrawal from the market, such as thalidomide, remoxipride, zimelidine⁴⁰³³, nefazodone (hepatic failure), and nomifensine, the latter being in clinical use for seven years. Thalidomide is making a comeback as a treatment for certain diseases, such as erythema nodosum leprosum, multiple myeloma, and wasting in AIDS. L-tryptophan was withdrawn because of an

⁴⁰²⁶ Jean Delay was the first president of the World Psychiatric Association (umbrella organisation of psychiatric societies) when it started in 1950.

⁴⁰²⁷ Term 'neuroleptic', to seize a neurone, coined in 1955 by Jean Delay.

⁴⁰²⁸ Synthesised by Paul Janssen (1926-2003) from meperidine.

⁴⁰²⁹ 'ein 5-Stellung basisch substituierte 5-H Dibenzo [b,e]-1, 4-diazepine'.

⁴⁰³⁰ Discovered in petalite by Arfvedson, 1817/8.

⁴⁰³¹ The urine of both patients and controls killed the animals!

⁴⁰³² Derived from chlorpromazine in the vain hope that it would be an antipsychotic drug.

⁴⁰³³ The first SSRI, created by Arvid Carlsson and co-workers in 1971 in Sweden.

association with the eosinophilic myalgia syndrome, which may have been due to contamination. Following the withdrawal of certain anti-appetite agents because of cardiac complications a new generation of anti-obesity drugs, including orlistat, took their place.

Chlordiazepoxide was introduced in 1960, and its more famous relative, another benzodiazepine⁴⁰³⁴, diazepam, became available three years later. Aesrinsky and Kleitman had discovered rapid-eye movement (REM) sleep in 1953.

Drug abuse has become a major universal problem since the 1970s,(Ghodse, 1995) although alcohol, which is legally available in most countries, is still the most problematic chemical, and particularly so in the former Soviet Union following relaxation of state controls.(Ryan, 1995) The changing fashions in the official handling of drug abuse (restricted methadone prescription practices changing to more liberal provision of methadone, condoms, and clean syringes) has been discussed by Berridge.(1999)

Community-based studies of psychiatric morbidity have become popular and large, e.g. two major US experiments: the *Epidemiologic Catchment Area Study* (> 20,000 adults aged 18 years and over) and the *National Comorbidity Study* (> 8,000 persons aged 15-54 years in 48 states).(Kessler et al, 1994)

Selected prominent names in psychiatric history⁴⁰³⁵

From Freud came Jung's 'analytic psychology' and Adler's 'individual psychology'. Other early influences included Abraham, Ernest Jones, Ferenczi, Reich, and Rank. The main American neo-Freudians were Fromm, Sullivan, and Horney. Anna Freud, Melanie Klein, Winnicott and Balint practised psychoanalysis and analytic psychotherapy, the first three with children, the last developing psychotherapy for primary care physicians. Bion and Foulkes were interested in group psychotherapy. Foulkes and Main developed family and marital therapy, with Main being interested in social therapy, as was Maxwell Jones. Other important contributors were Rogers (encounter), Moreno (psychodrama), Perls (gestalt), Lowen (bioenergetics⁴⁰³⁶ – influenced by Wilhelm Reich's 'character armour') (Lowen, 1958), and Janov (primal therapy). John Bowlby's⁴⁰³⁷ work on attachment, separation and loss was strongly influenced by Harlow's and Lorenz's simian and avian experiments respectively as well as separation of children from their parents in WW II and experience with conduct-disordered adolescents.

Famous Names in Psychiatric History (cf. O'Shea, 2001a)

Hippocrates, 470-400 BC, the Father of Medicine, should come first. He believed that insanity resulted from a disordered brain. When certain humours (from which comes 'good' and 'bad' humour: Wilson, 2004, p. 390) such as bile, or elements such as fire, were not in balance, illness ensued. Four bodily humours are described, each characteristic of personality type: black bile (from spleen, gloomy) – melancholia, blood – sanguine (optimistic, confident), yellow bile (from liver) – choleric (having a bad temper), and phlegm – phlegmatic (placid, apathetic). Five forms of madness followed: phrenitis – acute with fever; mania – acute without fever; melancholia – a chronic condition; epilepsy – seizures; and hysteria – a 'female' paroxysmal disorder. *Plato*, 427-347 BC, also asserted that mental life resided in the brain. *Aristotle*, 384-347 BC, however, placed mental life in heart, the brain being relegated to the lowly role of body temperature regulation.

Arateus of Cappadocia, c30-39 AD, opposed coercion and cruelty in the management of the insane. He also described various mental disorders, such as mania. Galen, 129-199 AD, subscribed to the Hippocratic views of madness and prescribed physical treatments such as diets, baths and, a not asocial habit in Roman times, vomiting.

St Thomas Aquinas, 1225-1274, held that internal (psychic) and external (environmental) causes of madness are in operation, a particularly modern view.

Paracelsus, 1493-1541, a Swiss, believed that anyone could suffer a mental breakdown. He promoted a medical approach to mental disorder, decrying the use of exorcism. A humane practitioner, he favoured psychotherapeutic measures and, aware of defences and other unconscious mechanisms, he emphasised the importance of personality factors in predisposition. His name for hysteria was chorea lasciva, which, like Freud, he believed had sexual origins.

Johann (or Johannes) Weyer, 1515-1588, German physician and author of *De Praestigiis Daemonum* (The Devil's Signs, 1563) rejected the notion of witchcraft and condemned any clergy who supported it. He attributed phenomena like hallucinations to a combination of natural and supernatural factors. Weyer stressed the need for careful clinical evaluation and the importance of the therapeutic relationship in psychotherapy.

William Cullen, 1710-1790, who was born in Lanarkshire but based in Edinburgh, coined the term neurosis. While his elaborate taxonomy of diseases of 1769 included 'neurosis', the latter embraced many unrelated conditions, e.g. hysteria, seizures, diabetes, and psychosis. Disease, according to Cullen was due to an excess or dearth of 'nervous energy'.

⁴⁰³⁴ BZD, so-called because of the fusion of **benzene** and **diazepine** rings.

⁴⁰³⁵ For convenience, these are listed alphabetically in tables: general and more *purely* psychoanalytical respectively.

⁴⁰³⁶ Posture has psychological meaning and exercises release tension with alleged underlying emotional change.

⁴⁰³⁷ British analyst (1907-90).

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Franz Joseph Gall, 1758-1828, founder of phrenology and a physician from Vienna who received the M.D. in 1785, tried to correlate personality traits with cranial contours⁴⁰³⁸. Being hounded from Vienna, he settled in Paris. His co-worker was Johann Gaspar Spurzheim, 1776-1832.



F J Gall

Franz Anton Mesmer, 1734-1815, invented 'mesmerism', a belief that 'animal magnetism', a type of cosmic force, was a useful therapy. Although disgraced following a French Royal Commission enquiry of 1784 (appointed by Louis XVI and consisting of Jean Bailly, Antoine Lavoisier, Joseph Guillotin, and Benjamin Franklin), his basic ideas were to rise again as hypnotism. (Gilman, 2004) *Phillippe Pinel*, 1754-1826, wrote the classic *Traité Médico-Philosophique Sur L'Aliénation Mentale ou La Manie*. He struck fetters from the inmates of Parisian psychiatric institutions, taking 6 years to remove them. He understood that the gastrointestinal tract was involved in the genesis of lunacy and employed laxatives and purgatives in their management, and he further held that a bout of diarrhoea could herald a remission. His treatment for premenstrual emotionality was early marriage and frequent pregnancies!



Phillippe Pinel

Benjamin Rush of Philadelphia, 1745-1813, was a Quaker who believed in phlebotomy. Madness, for Rush, was chiefly cerebrovascular in origin. A graduate of Edinburgh and a signatory of the American *Declaration of Independence*, Rush wrote first American textbook of psychiatry.

William Tuke, 1732-1822, a Quaker from York, founded the York Retreat in 1792 and became its manager cum treasurer. His grandson, Samuel, 1784-1857, published *Description of the Retreat* in 1813 and was made an honorary member of the Medico-Psychological Association (MPA), despite lacking a medical qualification. Samuel's youngest son, Daniel Hack Tuke, 1827-1895, studied law and medicine. He was physician to the Retreat and the York Dispensary, lecturer on mental diseases at York School of Medicine, governor of Bethlem, lecturer at Charing Cross Hospital, a founder of the Mental After-Care Association in 1879, editor of the *Journal of Mental Science*, and president of the MPA in 1881.

Alois Alzheimer, 1864-1915, Bavarian by birth, studied medicine in a number of German universities during 1882-87. He trained in neuropathology at Frankfurt, where he worked with Franz Nissl on histological stains (basophilic dyes like cresyl violet stain stacked rough endoplasmic reticulum, i.e. the Nissl substance of neurones). Later, he was invited to work with Kraepelin at Heidelberg. There, and later on in Munich, Alzheimer provided classical descriptions of the neuropathology of many conditions, such as Huntington's disease and Wilson's disease, and, in 1904, the first full neuropathological description of general paralysis of the insane. In fact his living reputation was based on his work on the pathology of syphilis⁴⁰³⁹ rather than on the condition that would bear his name. He reported the case of a demented 55-year-old woman⁴⁰⁴⁰ in 1906. Her brain showed loss of cerebral cortical neurones and thick, coiled masses of fibres within the cytoplasm of many nerve cells, a condition eventually bearing his name. Paul Blocq and Georges Marinesco had described senile plaques as far back as 1892.



Alois Alzheimer

⁴⁰³⁸ The novelist 'George Eliot' had her head shaved for phrenological examination!

⁴⁰³⁹ Syphilis was extremely common in asylums at that time and, perhaps because only 5% of people lived to age 65 years, Alzheimer's disease was a rarity.

⁴⁰⁴⁰ Mrs Auguste D, the D standing for Deter.

John Conolly, 1794-1866, the son of an Irishman, abolished restraints at Middlesex Asylum at Hanwell (later St Bernard's) in 1839. He wrote about the erection and administration of asylums in 1847, but appears to have changed his mind about the usefulness of asylums when he went into private practice! In fact, most asylum superintendents who tried Conolly's approach concluded that was 'idealistic and impractical', there being too many violent and suicidal acts to justify this 'utopian' vision. (Bynum ea, 2006, p. 199)

Emil Durkheim, 1858-1917, wrote the classic sociological study of suicide in 1897: *Suicide. A Study in Sociology*. According to Durkheim, suicide rates are low if society is integrated and regulated. Increased suicide rates occur if there is a lack of meaningful social interaction (norms lose their significance - egoistic suicide) or if individual interests are not subordinated to those of society (loss of guiding standards - anomie). They are also high if there is an expectation of self-sacrifice under conditions of excessive integration (as in war - altruistic) or if there is excessive social regulation (as in prison - fatalistic).

Havelock Ellis, 1859-1939, published an influential treatise on sexual disorders (1897) in England called *Sexual Inversion*.

Jean/Etienne Dominique Esquirol, 1772-1840, founded the first psychiatric teaching clinic in Paris. He emphasised the role of social and emotional factors in the genesis of mental ill health and wrote on the medical, hygienic and legal aspects of psychiatric illness. Esquirol also supplied the modern definitions of hallucination and illusion. He introduced the term *lypémanie* (Gk. *lype*, sadness), one of the many pseudonyms for depression.

Wilhelm Griesinger, 1817-1868, who was born in Stuttgart, was a renowned lecturer. He became professor of neurology and later neurology (after Moritz Romberg) and psychiatry (the world's first chair of psychiatry) in Berlin. Griesinger published *Pathologie und Therapie der Psychischen Krankheiten* (Pathology and Therapy of Mental Diseases) in 1845. He believed that mental illness is organic in origin and that all mental disorders are expressions of a single entity (Einheitspsychose: 'unitary psychosis'). It should be recalled that similar beliefs for the unitary nature of disease were sometimes held outside psychiatry. (Porter 2001 a, p.101)

Emil Kraepelin, 1856-1926, a German patriot and anti-Semite was responsible for the birth of modern psychiatric taxonomy and the concept of 'dementia praecox' (chronic poor prognosis schizophrenia with 'negative' symptoms⁴⁰⁴¹). He was aware of the problem of intermediate cases that do not fit into neat taxonomic categories. His close friend, Ernst Rüdin (1874-1952, Swiss born), participated in the Nazi racial hygiene programme. The concept of the 'praecox feeling', that invisible wall between patient and examiner, was introduced by the Dutch psychiatrist H C Rümke, 1893-1967, in 1941. Kraepelin lumped people with psychotic unipolar depression together with manic-depression cases and separation of unipolar from bipolar came later courtesy of Angst and others.



Emil Kraepelin

⁴⁰⁴¹ **Component syndromes of schizophrenia** predate Kraepelin. Some authors espouse a viral cause due to low reporting prior to 1800. Others suggest that schizophrenia became less common because of the decline in incidence of diseases like measles and diphtheria, suggesting either an immunisation effect or increased herd immunity. Foerstl (1989) quotes from case histories published prior to 1800, and Carpenter (1989) alludes to the bias against reporting poor prognosis cases, both disclaiming any novelty for schizophrenia. Schizophrenic patients may simply have died early before 1800, and 'lunatics' of the pre-asylum era were poorly classified and often lodged in prisons (psychosis is still not uncommon in prisons). Narrowing of diagnostic criteria over time or over-reliance on admission data may give a false impression that schizophrenia is disappearing. O'Shea and Falvey (1985) diagnosed schizophrenia in 42% of a sample of 50 in-patients based on information in an 1880 hospital ledger (schizophrenia accounted for 37% of admissions to the same hospital in 1980). Waddington and Youssef (1994) reported a fall in morbid risk in part of Ireland between those born during 1920-39 and those born after 1940, more so for females. Walsh (1992b), however, could find no evidence that schizophrenia became less common in Ireland over a period of 150 years. Nixon and Doody (2005) found no significant change in the incidence of schizophrenia in Nottingham from 1881-1994. In the 1880s Emil Kraepelin coined the term dementia praecox, roughly covering modern chronic schizophrenia. Chronic schizophrenia may develop *de novo* or follow a history of acute schizophrenia. Kraepelin viewed the chronic condition as a dementing process with a uniformly poor prognosis. Eugen Bleuler, in 1911, widened the concept to include cases of lesser severity, dropped the idea of dementing illness, felt that some cases fared not too badly, and called the subsumed collection of syndromes the group of schizophrenias. Bleuler's concept of schizophrenia bears more of the hallmarks of a dimensional than a categorical approach, thus blurring the boundaries with normal experiences. (Nasrallah & Smeltzer, 2002, p. 18) Rümke of the Netherlands introduced the term 'praecox feeling' in 1941 to denote the perceived psychological gap between physician and patient.

⁴⁰⁴¹ According to Jablensky (2003, p. 203), the attributes that define schizophrenia are inferential and are highly dependent on the patient relating private mental activity, there being no 'test' for schizophrenia. The word *schizophrenia* comes from two Greek words meaning a disconnection or splitting of the psychic functions and has no connection, except in popular fiction, with the Jekyll and Hyde character, the latter being more likely a psychopath. Bleuler's 'schizophrenia' is reminiscent of Kraepelin's 'intrapsychic ataxia' (splitting/fragmentation of functions of the mind). According to ICD-10, *psychosis* 'simply indicates the presence of hallucinations, delusions, or a limited number of several abnormalities of behaviour, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behaviour'.

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Henry Maudsley, 1835-1918, who hailed from Yorkshire, offered money to London County Council for the construction of a hospital that would be a medical school cum psychiatric hospital that treated patients with early illnesses either as in- or out-patients. Maudsley died before the hospital, which bears his name, opened in 1923. Among the hospital's famous medical men was Sir Aubrey Lewis. In 1865, Maudsley was able to get psychiatry placed on the curriculum of the University of London; later, a single question on the subject appeared in the final medical paper. He became professor of medical jurisprudence at University College London in 1876. He is commemorated in an annual Maudsley Lecture. Delamothe, in 1988, described Maudsley as British psychiatry's greatest exponent of the theory of degeneration: some past 'unnatural excitement' of civilisation left a genetic taint which deteriorated across generations, eventually destroying descendants; alcoholism, masturbation and syphilis were 'implicated' (Noguchi and Moore demonstrated the spirochaete in syphilitic brain in 1913). Maudsley became a semi-recluse toward end of his life, probably to look after his dementing wife.

Benedict-Augustin Morel, 1809-1873, the famous French alienist who was influenced by an apparent explosion of mental illness and fears of declining human quality, hypothesised that hereditary *degeneration* lay behind mental illness. Neurotic or drunken parents bred mentally alienated children. The latter bred imbeciles who in turn bred sterile offspring. Kraepelin translated morel's term *démence précoce* as dementia praecox.

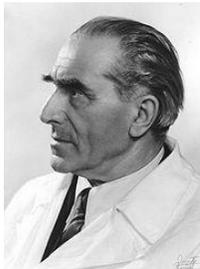
Eric Berne, who died in 1970, was a graduate of McGill University in Montreal. He was the founder of transactional analysis (TA). Berne taught that we have three communication levels or 'ego states', namely the 'parent', the 'adult', and the 'child'. The therapist analyses the transactions between these states, e.g. the adult in one person talking to the child in another. The 'life script' was likened to a piano player who thought he was making music whereas the real 'player' was a drum inside the instrument, i.e. we are programmed to act in a certain way from an early age. Therapy supplies the solution to a dilemma in the form of an 'antiscrypt'. Berne served in the US Army Medical Corps during the Second World War with the rank of major. He became a consultant in psychiatry and neurology to the Surgeon General. His published works include *The Mind in Action* and *Games People Play*. He also wrote *A Layman's Guide to Psychiatry and Psychoanalysis* (Penguin).

Eugen Bleuler, 1857-1939, used the term schizophrenia in 1911 to cover a heterogeneous group of disorders. He considerably widened Kraepelin's concept of dementia praecox. A variety of prognoses then became possible in schizophrenia. Bleuler's pupils included Jung and Ernest Jones. Bleuler broke with psychoanalysis, made a special study of the inner world of the psychotic, and was the first to use the terms 'autism' and 'ambivalence'. His son, Manfred, 1903-1994, professor of psychiatry at Zurich, performed an ultra-long follow-up of schizophrenic patients of the Burghölzli and reported that the condition's progress tended to plateau after the first tumultuous few years.



Eugen Bleuler

An Australian, *John FJ Cade*, 1912-1980, spent three and a half years as a POW of the Japanese, later taking charge of a veterans' psychiatric hospital. His animal studies revealed a calming effect for lithium. Cade introduced lithium to psychiatry in 1949 - Hammond made this recommendation back in 1871 - and demonstrated its efficacy with the start-stop-start technique. Earlier, unsuccessful medical uses of lithium included the treatment of gout by Alfred Garrod (1859) and epilepsy (bromide salt), and as a salt substitute in cardiac cases in the 1940s in USA, the latter leading to many deaths which set back its use in America for many years. *Ugo Cerletti*, 1877-1963, who was born in Lombardy, worked with Franz Nissl and Alois Alzheimer. He demonstrated the origin of neuroglial fibres from glial cells and found senile plaques in elderly normal brains. Cerletti became professor of neuropsychiatry at Bari in 1925 and in Rome in 1935. He provoked canine convulsions in a study of the genesis of epilepsy (Ammon's horn). With Lucio Bini, 1908-1964, he gave electric shocks to animals. In April of 1938 he gave the first course of ECT (to a 39-year-old man from Milan), and noted that cardiazol-induced hyperexcitability did not occur with ECT; also, recovery was smoother with electricity. In 1950 he suggested that ECT released 'acrogonine' in the brain.



Ugo Cerletti

The Norwegian, *Asbjørn Følling*, 1888-1972, described phenylketonuria in 1934 after parents had asked his advice on their two mentally retarded children. Many colleagues felt that he should have received the Nobel Prize.

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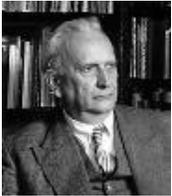
A Frankfurter whose family immigrated to England when he was a toddler, *Max Hamilton*, 1912-1988, is best remembered for his psychometric approach to the assessment of depressive illness, especially his *Rating Scale for Depression*. He qualified in medicine from University College Hospital in 1934, joined the RAF during WW2, and later worked at the Maudsley, King's College Hospital, and University College London. He worked at the latter with Sir Cyril Burt, 1883-1971, a psychologist and disciple of W. McDougall, 1871-1938. Hamilton worked at Springfield Hospital, south London, where he continued research into reliable objective assessments of affective variables. His other appointments included senior lecturer (1953) and then professor and head (1963-77) of psychiatry at the University of Leeds, and president of the British Psychological Society (1973).

The Parisian psychologist-turned-medical man who studied under Charcot (see Charcot's picture below) at the Salpêtrière, *Pierre Janet*, 1859-1947, introduced the concept of 'dissociation' ('separation' of one part of the mind from another), an important defence in hysterical states such as amnesia, fugue, twilight state, and so-called 'multiple personality'. He believed that more primitive psychological functions appear when higher ones were impaired.



Jean-Martin Charcot (1825-1893)

Karl Jaspers, 1883-1967, was born at Oldenburg in Germany. He met Nissl, Ranke and Mayer-Gross at Heidelberg, where he became professor of psychology. His classic, *General Psychopathology*, was first published in 1913. Jaspers died while professor of philosophy in Basel.



Karl Jaspers

The son of a Bavarian Lutheran pastor, *Karl Leonhard*, 1904-1988, described cycloid psychosis, he characterised the defective conditions of schizophrenia, differentiated bipolar from unipolar affective disorder, and defined frontal lobe syndrome. Leonhard was an early exponent of behaviour therapy and a pioneer in the study of human sexuality and human expressive behaviour.

Sir Aubrey Lewis, 1900-1975, the son of London Jewish watchmaker, was born in Adelaide Australia and studied psychiatry in America and Germany. He arrived in England in 1928 and joined the Maudsley. Lewis led part of the Maudsley to Mill Hill in 1939 and attracted Hans J Eysenck (1916-97) and Maxwell Jones to work with him. He became professor of psychiatry at the University of London (1946), succeeding Mapother. He united the Bethlem and Maudsley hospitals to form the Institute of Psychiatry. Lewis is best known for his social inquiries (including industrial health), metabolic studies, and his influence on a generation of psychiatrists.

The Swiss psychiatrist, teacher of Aubrey Lewis, and spouse of the first American psychiatric social worker, *Adolf Meyer*, 1866-1950, founded the 'psycho-biological' approach to psychiatry at John Hopkins: every aspect of the client, including physical, rearing and social, had to be considered. His special interest was preventive psychiatry. Various illness categories were described as 'reaction-types', e.g. schizophrenic reaction-type. Modern psychiatric history taking and examination of the mental state date to Meyer in 1918.

'*Egas Moniz*' (born Antonio Caetano de Abreu Freire in Portugal), 1874-1955, professor of neurology in Lisbon, took the name of a hero against Moors! He performed first frontal lobotomy (through hands of Almeida Lima, the neurosurgeon) in 1935. His efforts were rewarded with the Nobel Prize in 1949. Moniz also invented cerebral angiography. He held the chair of neurology in Lisbon. Aged 65, he was shot by a leucotomised schizophrenic patient, but survived!



Lobotomy

Eliot Slater, 1904-1984, joined the Maudsley in 1931 where he was encouraged by Aubrey Lewis and received statistical advice from R A Fisher. He undertook genetic research in 1930s Munich. Slater married Lydia Pasternak, daughter of the Russo-Jewish novelist, was a co-author of *Clinical Psychiatry* (with Mayer-Gross and Martin Roth), and proposed a monogenetic theory of schizophrenia that

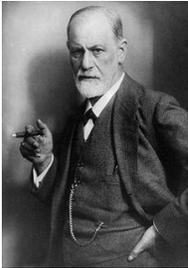
was later supplanted by a polygenic paradigm. He established the famous Maudsley twin register; viewed hysteria as a non-genetic, communicative, problem; reported on the schizophrenia-like psychoses of temporal lobe epilepsy; was editor of the *British Journal of Psychiatry* (1961-72); and received a PhD when 77 years old for work on Shakespeare's plays (comparing the frequency of unusual words). Slater resigned from the National Hospital of Nervous Diseases, Queen Square, after neurologists questioned the scientific maturity of psychiatry! He has been described as "an intellectual giant...yet capable of bizarre judgement, as when he devoted the whole of the first number under his editorship of the *British Journal of Psychiatry* to his own work".

Chief players in psychoanalytic history (O'Shea, 2001b)

Men

Sigmund Freud (1856-1939), father of psychoanalysis and a neurologist was born in Freiburg, now Pribor, in Moravia, for Jacob Freud and Amalia Natanson. Sigmund's half-brother Philip made Amalia pregnant, which may have been influential in the origin of the Oedipus Complex. A refugee of the Third Reich himself, four of Freud's five sisters died in Nazi camps. Early on, Freud published neurological and neuroanatomical works, including a monograph on aphasia that Erwin Stengel (1902-1973) translated into English in 1953. Freud married Martha Bernays, studied under Charcot and published, with Josef Breuer (1842-1925: of reflex fame) *Studies on Hysteria* in 1895. He was possibly addicted to cocaine; his colleague, Carl Koller (1857-1944), discovered its local anaesthetic properties. In 1894 and 1899, he had nervous breakdowns. During this period, immortalised in *Traumdeutung* (1900), Freud corresponded with Wilhelm Fliess, inventor of the concept of a nasal reflex neurosis. Freud analysed himself, so starting a family of analysts, and each member thereafter being analysed by someone who was analysed by someone else. Freud's claims for cures have been much criticised in recent years, with talk of former patients dying in mental hospitals. He provided a framework allowing the conceptualisation of mental processes where there had previously been only demonology and degeneracy. Mapother believed that Freud was more of an artist than scientist. Freud may have got major ideas from the German philosopher Friedrich Nietzsche (1844-1900). Merskey attacked Freud's idea of 'repression', believing that it has been used unethically to produce false memories of sexual abuse in infancy.

Freud suffered from carcinoma of maxilla and palate from 1923 and received repeated surgery and radiotherapy. On September 23, 1939 in London, his physician and friend Max Schur administered an overdose of morphine at Freud's request.



Sigmund Freud

Alfred Adler (1870-1937) was born in Vienna, had rickets as a child, trained as an eye specialist, converted to Christianity from Judaism, and died at Aberdeen. He met Freud eight years before Jung. He later broke with Freud, rejected libido theory, founded 'individual psychology', and taught that contemporary environmental factors were more important than sex in determining human behaviour. Adler tried to understand how an individual arrived at his present life-style. Current problems were given due attention in therapy. According to Adler, we all have an 'inferiority complex' and compensate for this via the 'masculine protest'.



Alfred Adler

Carl Gustav Jung (1875-1961) leader of the school of 'analytical psychology' and a pastor's son, was born in Switzerland and worked with Bleuler at Zurich. Janet was one of his teachers. Jung corresponded with Freud from 1906 and met him in Vienna a year later. From 1908 to 1914 he was Freud's closest disciple. Jung was concerned with the inner world of fantasy and with interpreting unconscious material in dreams and artistic production. He spoke of a 'personal unconscious', containing unique drives and memories, and 'collective unconscious', an inherited, deeper level composed of collected ancestral memories: we are programmed to act in archetypal ways (e.g. the 'hero'). Well-known archetypes (ancient stereotypes) include the 'persona', our social mask, the 'anima', the inner soul-self that is in touch with the unconscious, and the male counterpart of the anima, the 'animus', and the 'shadow', the latter containing unconscious tendencies that must be 'revealed' in therapy. Jung wrote about 'introversion' and 'extraversion', whereby libido is directed inward or outward. The 'Self's' objective is to maintain an integrated, stable personality. 'Individuation' is the struggle for self-realisation, this process being disturbed in neurosis.



Carl Jung

Harry Stack Sullivan, (1892-1949), born Norwich, New York, stressed interpersonal dynamics and he defined personality in terms of relative and enduring patterns of recurring interpersonal behaviour. Sexual problems are but one aspect of a person's difficulties. Treatment should be centred on the patient-therapist relationship. Sullivan discussed everyday events with his clients and used pointed questions and provocative statements in preference to theory-based interpretations. A homosexual himself, Sullivan believed that patients need a same-sexed therapist.

Women

Bertha or Elsa Pappenheim (Anna O: 1859-1936) is the best known patient of Freud and Breuer. Lessons learned during her treatment were used in the writing of *Studies on Hysteria*. She would later become interested in separation anxiety. Merskey argues she had a depressive disorder, morphine and chloral hydrate dependence, hysterical conversion, and cyclothymia! Other patients of Freud included *Ida Bauer (Dora)* and *Sergej Pankejeff (Wolf Man)*.



Anna O

Anna Freud CBE, (1891-1982 –**picture on right**), a school teacher and child analyst, was Freud's youngest child and closest disciple. She observed children at play, was analysed by her father, had no medical qualification, and remained a spinster. Her main contribution was *The Ego and the Mechanisms of Defence*, developed from her father's work.

Karen Horney (1855-1952), a native of Hamburg, rejected Freud's 'penis envy' and blamed woman's inhibition on the strictness of her upbringing. She held that aggression is not inborn but learned.

Melanie Klein (1882-1960) placed the Oedipus complex in infancy! Objects, for the infant, are good or bad; part is confused with whole: breast is equated with mother. At about six months the baby is biting objects (oral sadistic stage) and fears mother will punish him for this hostility. Through denial and projection (attributes of self are imagined to belong to others) the infant assumes a 'paranoid position'. Ambivalence towards objects may lead to guilt and a 'depressed position'. Klein's 'projective identification' (subject projects part of self onto object, then identifies with object or elicits response in object corresponding to qualities of the projection) was further developed by Wilfred Bion (1897-1979). Klein's first 'patient' was her own daughter, Melitta Schimberg, who later became an analyst working with delinquent adolescents and who resented her own mother's intrusions so early in life!

Helene Deutsch (1884-1982) wrote *The Psychology of Women* and challenged Freud's dictum that the 'enigma of the female' could not be understood by either sex.



Concluding comments

While the standing of psychiatry improved due to its efforts at early treatment of military casualties and better selection for military roles in World War Two, psychiatrists greatly overestimated the number of psychiatric victims from the Blitz. (Parker, 1990) Derek Russell Davis performed his Cambridge cockpit experiments during the war in order to test the psychological stresses and fears of pilots. Lieutenant General George Patton Jr found that it did not pay to slap a 'psychiatric casualty' and call him a 'goddamned coward' on August 3 1943 near Palermo, Sicily! (Shephard, 2002, p. 219) It cost him his command.

The exodus of psychiatrists from Nazi Germany is discussed by Peters. (1996) Ernst Rüdin (1874-1952), the Swiss psychiatrist, geneticist and eugenicist, gave his support to Hitlerite policies (**picture on left**). At least 140,000 institutionalised psychiatric patients died of mistreatment or starvation in Germany during the Nazi era. (Schmiedebach, 1997, p. 115) Post-war exposure of Soviet abuse of psychiatry, leading to the withdrawal of the *All-Union Society of Neurologists and Psychiatrists* from the WPA in 1983, revealed a regime dependent on styling their detractors 'mad' (or suffering from 'sluggish progressive



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schizophrenia' – brainchild of Andrei Snezhnevsky [1904-1987] of Moscow's Serbsky Institute) rather than 'bad'!(Bloch & Reddaway, 1977; Tomov, 1999) Concern was raised over the misuse of 'sluggish schizophrenia', a slowly evolving type of schizophrenia described in the USSR, and its potential use to label democrats.(Merskey & Shafran, 1986) Readers were also disturbed by the haunting images of inmates of the 'Psychopathic Colony' on the Dodecanese island of Leros⁴⁰⁴² being collectively hosed down in open courtyards.(Henderson, 1999) Even in 2003, patients in Slovenia, Hungary, Slovakia, and the Czech Republic were being kept in padlocked, caged beds!(Krosnar, 2003)

Conversion hysteria was not uncommon in Western soldiers in World War One and in Indian servicemen in World War Two, but was still not uncommon in Indian villages toward the close of the twentieth century.(Mumford, 1999) However, Shorter (1997) has described both chronic fatigue (ME, Royal Free disease) and multiple chemical sensitivities as the 'grandchildren' of neurasthenia⁴⁰⁴³ (the latter being retained in the ICD because of its use in countries such as China): old disorders may simply don the cloak of modernity. New disorders have also stepped in to replace the afflictions of yesteryear, e.g. AIDS⁴⁰⁴⁴ and borderline personality disorder; the first case of variant CJD⁴⁰⁴⁵ in Ireland was reported by St Vincent's Hospital, Elm Park, in June, 1999.

AIDS timeline

1876	Moritz Kaposi (1837-1902) described the cancer now called after him
1981	Centers for Disease Control and Prevention in USA report 5 cases with strange immune deficiency
1982	Terence Higgins Trust launched in London
1984	HIV identified in American and French laboratories
1985	Actor Rock Hudson (b. 1925) dies from AIDS
1986	Needle exchange programme in UK
1987	Robert Gallo (USA) and Luc Montagnier (France) recognised as co-discoverers of HIV
1987	AZT, first antiretroviral drug, licensed
1991	Queen rock band star Freddie Mercury (b. 1946) dies from AIDS
1993	American black tennis star Arthur Ashe (b. 1943) dies from AIDS ⁴⁰⁴⁶
1996	UNAIDS ⁴⁰⁴⁷ set up
1998	American trial of vaccine for HIV
2006	Over 25 million deaths from AIDS since 1981
2008	Françoise Barré-Sinoussi ⁴⁰⁴⁸ and Luc Montagnier ⁴⁰⁴⁹ of France share Nobel Prize for discovery of HIV ⁴⁰⁵⁰

Modern forms of psychotherapy such as interpersonal psychotherapy (Klerman et al, 1984) and Beck's cognitive therapy (Beck et al, 1979) have largely replaced longer-term analytic approaches. Beck's ideas were not new. Epictetus (c. 55-135 AD), a Greek stoic philosopher and former slave, believed that good came from restraining the passions and that we are not upset by things but by the meaning we attach to them. Albert Ellis (1913-2007), the American psychologist who developed rational emotive behaviour therapy in the mid-1950s, approached therapy with the armour of reason and persuasion in contrast to Beck's use of theories that are tested by the patient in order to gauge their accuracy. Donald Meichenbaum of Ontario developed self-instructional training during the 1970s aimed at modulating impulse control problems through verbal self-regulation.



Asper colony during the middle ages and an Italian and Greek prisoner-of-war camp. Approximately 3,000 chronic them intellectually handicapped, were sent their chained in Greek naval ships!(Browne, 2008, p. 157)

Neurasthenia was described by George Beard in 1869.

⁴⁰⁴⁴ The likely origin of HIV-1, a lentivirus (slow to multiply and cause damage), are the simian immunodeficiency viruses (SIVs). Such viruses have been isolated from a western equatorial Africa subspecies of chimpanzee (*Pan troglodytes troglodytes*). Hunters and eaters of raw bush meat may have picked up the virus.

⁴⁰⁴⁵ Creutzfeldt-Jakob disease described 1920-1 by Germans Hans Creutzfeldt (1885-1964) and Alfons Jakob (1884-1931). The concept of a 'slow virus' as the cause of scrapie dates from 1954 and the Icelandic virologist Björn Sigurdsson (1913-59).

⁴⁰⁴⁶ Acquired via blood transfusion given for cardiac surgery.

⁴⁰⁴⁷ Joint UN Programme on HIV/AIDS.

⁴⁰⁴⁸ Born 1947.

⁴⁰⁴⁹ Born 1932.

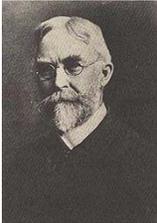
⁴⁰⁵⁰ 2008 Nobel Prize was shared with Harald zur Hausen (Germany), discoverer of link between HPV and cervical cancer.

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Insurance-led changes in America added another nail to the coffin of full psychoanalysis. Also, factors common to all psychotherapies may be independent of school of origin.(Storr, 1979) In practice, public psychotherapy provision is poor.(Amies, 1996) Post-traumatic stress disorder, the term dating from studies of Vietnam veterans, is now viewed as stemming from a wide variety of combat and not-combat situations, including ‘ethnic cleansing’.(Weine et al, 1995)

Transcranial magnetic stimulation, which has been used by neurologists for some time for various purposes, such as the mapping of cortical function, is now being studied by psychiatrists as a treatment for depression. Whether it will replace ECT remains to be seen.(Reid et al, 1998)

Pneumoencephalography was the first method used to visualise living brain. Introduced by Dandy, an American, in 1918, it involved injecting a gas such as air into the cerebrospinal fluid spaces and then taking X-rays. Using this technique, Jakobi and Winkler (1927) described ventricular enlargement in schizophrenia. Purcell described the phenomenon of magnetic resonance (Nobel Prize, 1952) in 1946, two years before the first successful measurement of cerebral blood flow using nitrous oxide.(Kety et al, 1948) 1980 saw the first clinical demonstration of intracranial pathology using magnetic resonance imaging (MRI). (Hawkes et al, 1980) Computerised tomography had been introduced earlier.(Hounsfield, 1973) 1993 saw the discovery of the gene for Huntington’s disease⁴⁰⁵¹, the genetic abnormality being similar to those found in the fragile X syndrome, spino-bulbar muscular dystrophy, and myotonic dystrophy.(Huntington’s disease Collaborative Research Group, 1993)



George Huntington (1850-1916)

The polymerase chain reaction (PCR), described in the mid 1980s and employed in the amplification of nucleic acid sequences, was a major boost to genetic research. The mouse genome was thoroughly mapped (Vincente & Kennedy, 1997) and then the human genome revealed many of its secrets. Cloning and somatic gene therapy, the introduction and expression of recombinant genes in somatic cells for the purpose of treating disease, have arrived.(Wise, 1997) Concern was expressed in May, 1999 that ‘Dolly’, the cloned sheep, was showing signs of excessive genetic, but not somatic, ageing - did one have to add six years, the age of the ewe from whose somatic cell ‘Dolly’ was cloned, to the new sheep’s age?(Wilmut et al, 2000) Trials of gene therapy were suspended in France in 2002 when a boy being treated for X-linked severe combined immunodeficiency syndrome (SCID) developed leukaemia; in the same year, an 18-month-old boy was successfully treated for X-linked SCID in London: bone marrow cells are deliberately infected with modified retrovirus (virus carries the corrective gene for a functioning immune system). Lack of power to compel discharged treatment in the community to comply with treatment is a concern for modern psychiatry.(Dillner, 1995; O’Shea, 1995) Many states in the USA have provisions for legally requiring a patient to comply with extra-mural treatment – so-called ‘outpatient commitment’: authorities may seek and detain the patient when medication appointments are missed.(Rand & McKee, 1998) The *Mental Health (Patients in the Community) Act 1995* in Britain introduced supervised discharge orders, although it does not provide effectively for compulsory adherence to treatment.(Pinfold et al, 1999) According to Burns and Priebe (1999), psychiatrists must lead in advising governments about services;

⁴⁰⁵¹ An abnormally long trinucleotide repeat sequence.

otherwise the vacuum will be filled by pressure groups and voluntary agencies whose convictions may exceed the evidence for feasibility or value of their proposals. A strong argument against an institutional basis for negative symptoms⁴⁰⁵² is the finding that these symptoms persist for at least nine years after discharge from hospital.(Johnstone et al, 1981) Recent escalation of the suicide rate in young males poses enormous medical, political, and social dilemmas, not all of which can be redressed by psychiatrists.(Porter, 1997) although there are signs of a reversal in this trend.(McClure, 2000) Shorter (1997) attributes the apparent increase in the incidence of 'depression' to a widening of its definition to include normal variations in mood and habits. A law of Northern Territory, Australia, allowing the terminally ill to take their own lives - using a computer-controlled lethal injection - was overturned in March, 1997; the Dutch authorities allow physician-assisted suicide, despite lack of statutory provision, and Belgian doctors failed to resist its introduction; and the American Supreme Court passed down decisions about physician-assisted suicide to the state legislatures, although the battle between the latter and the former continues.(Steinbrook, 2002)

In 1997, the Liggett Group, the smallest US tobacco company and makers of *Chesterfield* cigarettes, agreed to settle all claims against them⁴⁰⁵³ in return for immunity from litigation, thus opening an ever-widening legal attack on the industry.(Beecham, 1997)

Richard Speck was sentenced to death in 1996 for slaying eight nurses in Chicago, despite having the XYY sex-chromosome constitution. The state of California passed the first antistalking law in 1990.

The Editor of the *Irish Medical Journal*, noting that out-patient clinics in the Republic of Ireland in 1996 were held at 251 locations with 233,512 attendances, described the situation as 'a staggering burden on our psychiatric community services'.(Editor, 1998) According to Jones (1999), those who devise mental health policies are financially motivated and the diversification of services inherent in extra-mural psychiatry hindered the collection of meaningful information on service efficiency.

According to Thornicroft & Maingay (2002) mental illness accounted for 12.3% (and rising) of the global burden of disease; it also accounted for 31% of all years lived with disability; only one in four countries had mental health legislation; 28% of countries had no specified mental health budgets; and one-third of all people resided in nations that invested less than 1% of the total health budget in mental health.

We are embracing the era of Health-Maintenance Organisations,(HMOs) evidence-based medicine (but which evidence to use?), subcellular third-messenger systems, freedom of information and 'transparency', 'key workers', rising power in the para-medical professions ('You prescribe and I'll treat!'), disturbingly high levels of reported child sexual abuse, the *Protection for Persons reporting Child Abuse Act 1998* (Ireland), *Viagra* (sildenafil - when combined with *ecstasy* it is sold on the streets as sextasy), cybersex (teledildonics - virtual sex computer programmes), ambivalence over community-based psychiatry,(Bartlett & Wright, 1999; Moncrieff & Smyth, 1999) comorbidity, ageing populations, and a long list of bewildering changes, not the least strange being a proposal to pay patients to take their medication.(Giuffrida & Torgerson, 1997) By way of personal reassurance, the author is reminded of the theme⁴⁰⁵⁴ of an article published in 1970,(Allderidge, 1970), and will avoid empty prognostication.

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⁴⁰⁵² The clinical poverty syndrome.

⁴⁰⁵³ I.e. that cigarettes are addictive and harmful.

⁴⁰⁵⁴ 'Hospitals, madhouses and asylums: cycles in the care of the insane'.

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Appendix

It is often assumed that readers are classic scholars! Alas this facility is not as common as heretofore. For the benefit of those who are bewildered by the use of Greek letters and Roman numerals in the literature the editor has included the following guide:

Commonly used Greek letters

Αα [Alpha](#), Ββ [Beta](#), Γγ [Gamma](#), Δδ [Delta](#), Εε [Epsilon](#), Χχ [Chi](#), Κκ [Kappa](#), Λλ [Lambda](#), Μμ [Mu](#), Ππ [Pi](#), Φφ [Phi](#), Σσς [Sigma](#), Θθ [Theta](#), Ττ [Tau](#), Ωω [Omega](#)

Less commonly used Greek letters

Νν [Nu](#), Ξξ [Xi](#), Οο [Omicron](#), Ρρ [Rho](#), Ζζ [Zeta](#), Ηη [Eta](#), Υυ [Upsilon](#), Ιι [Iota](#), Ψψ [Psi](#)

Roman numerals

I = 1, II = 2, III = 3, IIII or IV = 4, V = 5, VI = 6, VII = 7, VIII = 8, IX = 9, X = 10, XI = 11, XVI = 16, XX = 20, L = 50, LV = 55, LIX = 59, C = 100, CL = 150, M = 1,000, MMX = 2,010

A numeral with a line over it means that you multiply by 1,000, e.g. X with a line over it = 10,000