Textbook of Psychiatry

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Contents

1 Diagnosis & Classification

This chapter explains what is meant by a psychiatric diagnosis, methods for making diagnoses, and aspects of diagnostic reliability, validity, and utility. Psychiatric and somatic comorbidities are elucidated. It includes a section on the influence of traditional medicine for most of the world's population. It provides an overview of diagnostic interviews and screening questionnaires.

Historical development of psychiatric diagnoses

What is a diagnosis? The word stems from *dia* (Greek) meaning through and *gnosis* (Greek) meaning knowledge, or the establishing of the nature of a disease. Making diagnoses is as old as medical history.

Diagnoses described in ancient times still hold, for example clinical depression was described by *Aretaeus* (81-138), who practiced medicine in Rome and Alexandria. The physician *Ibn Zohr-Avenzoar* (1092-1162) in Morocco described in his clinical treatment guideline acute delirium, melancholia and dementia among other psychiatric disorders, and also reported the first known account of suicide in melancholics. In 1286, *Le Maristane* (hospital) Sidi Frej was built in Fes, Morocco, for psychiatric patients, and was a model for the first mental asylum in the western world in Valencia, Spain, in 1410.

The term *neurosis* was created by the Scottish neurologist William Cullen in 1769 to label patients with nervous symptoms without an obvious organic cause. Chronic alcoholism was described by Magnus Huss in Stockholm in 1849. The German psychiatrist and neuropathologist Wilhelm Griesinger (1817-1868) laid the modern foundation of psychiatric classification in 1845, publishing a monograph on diseases of the brain. He proposed a unitary concept of psychosis. Subsequently Emil Kraepelin in Munich (1856-1926), the forefather of contemporary scientific psychiatry, split this unitary psychosis into two distinct forms based on symptom patterns that he called manic depression and *dementia praecox*. The Swiss psychiatrist Eugen Bleuler (1857-1939) renamed the latter schizophrenia, having determined that this disorder did not necessarily progress to dementia.

French psychiatrists made important early contributions to psychiatric diagnoses, such as Tourette's syndrome, first described in 1885 by the neurologist Giles de la Tourette (1857-1904). He also described anorexia nervosa in 1890. Paul Hartenberg (1871-1949) eloquently described social anxiety disorder in his monograph *Les Timides et la timidité* in 1901.

After the second world war, the validity of psychiatric diagnoses was questioned by the United States military, since many recruits had been considered unfit for soldier duty by psychiatrists. Many combat soldiers were discharged on psychiatric grounds. There was no

consensus on how to make psychiatric diagnoses. In the absence of an agreed classification, epidemiological research was not possible.

There were many thought leaders on the merits of making diagnoses. Sigmund Freud (1856-1939) postulated unconscious conflicts as the source of mental ill health, while the Swiss-born psychiatrist Adolf Meyer (1866-1950), influential in the United States, advocated that such ill health was a personality reaction to psychological, social, and biological factors. In Scotland, Ronald Laing (1927-1989) launched the "antipsychiatric" idea in 1955 that psychosis was a reaction to a cold family environment that produced a false "id," for example the case of the schizophrenogenic mother. He argued that psychiatric diagnoses rested on false grounds in that it was solely based on the patient's conduct without external validators. The Hungarian-born American psychoanalyst Thomas Szasz (1920-) advanced the idea that psychiatric disorders are a myth, or social branding. He was embraced by the scientology movement in 1968 whose originator L. Ron Hubbard (1911-1986) in 1950 created the business of dianetics, the doctrine of the Church of Scientology, as an alternative to psychoanalysis.

The 1950s and 1960s brought critique of psychiatric diagnoses, a movement that coincided with the civil rights movement of the 1960s, and that particularly targeted the grounds for involuntary commitment to psychiatric care by means of diagnoses. When, in an experiment, several psychiatrists were asked to diagnose the same patient, it was obvious that they represented different schools of thought that did not share a common set of definitions. This challenging of the intellectual ground of psychiatry had profound effects on the allocation of resources, shifting from institutionalization to outpatient voluntary care in the United States and in Europe. In Italy all involuntary care was declared unlawful in 1978.

Two psychiatrists at Washington University in St. Louis then decided to bring sense into psychiatric diagnoses: Samuel Guze (1923-2000) and Eli Robins (1921-1995). In 1970 they published a paper on a criteria-based diagnosis of schizophrenia. This seminal paper became the intellectual basis for the 3rd version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) that was published in 1980 by the American Psychiatric Association. This fundamentally new classification was based on a consensus of clinical criteria. Also, the DSM-III did not assume etiological factors; it was based on a consensus among academic psychiatrists about the typical symptoms of a disorder and its prognosis. In 1987 and in 1994 this classification was revised, based on 150 literature surveys, and 12 field studies with more than 6000 diagnostic interviews. Work on its 5th version is ongoing, and it is to be published in 2012 (`http://www.psych.org/MainMenu/Research/DSMIV/DSMV.aspx)`.

The DSM classification applies 5 perspectives on a patient: Axis 1 disorders (for example major depressive episode, anorexia nervosa), Axis 2 personality disorders, and neurodevelopmental disorders), Axis 3 somatic disorders (for example diabetes mellitus, traumatic brain injury), Axis 4 current stressors (for example having been raped, bereavement), and Axis 5 global assessment of function.

One current ambition in revising the DSM classification is to pay more attention to ethnicity in understanding how symptoms may present. Gender differences will also be elucidated. The most important change in DSM-V will be the inclusion of dimensions in diagnoses; for example, how severely ill is a patient with schizophrenia or depression.

By international convention most countries use the International Classification of Diseases (ICD) in making all diagnoses (somatic and psychiatric) in routine health care. This classification is produced by the World Health Organization. The current ICD-

10 classification is quite similar to that of DSM-IV. The WHO is currently working its 11th revision of the ICD. With regard to the psychiatric diagnoses there is a joint effort with the DSM-V developers to use similar principles and standards. The revision process was formulated in 2007 and the draft version will be tested in field trials (`http://www.who.int/classifications/icd/ICDRevision/en/index.html`).

These efforts have advanced the reliability of psychiatric diagnoses to standards similar to those of other disciplines. Methods for external validation have emerged in recent years. For example, functional magnetic resonance imaging (fMRI), and other in vivo imaging techniques, allow one to study how the amygdala reacts to an anxiety provocation in a subject with an anxiety disorder. Imaging techniques reveal disturbed CNS networks in subjects with schizophrenia, and pronounced structural aberrations in the lateral and medial parts of the temporal and frontal lobe. Untreated depression has been shown to cause cerebral shrinking. The efficacy of serotonergic medications depends on neurogenesis. Latency to rapid eye movement sleep is correlated to clinical symptoms of depression. Amyloid, a protein in the plaques in Alzheimers disease, has been detected in vivo in patients in a PET study. The effect of antipsychotic and antidepressant drug treatments can be correlated to symptom reduction, cerebral blood flow, and brain metabolite ratios.

Psychiatric comorbidity

The criteria in the DSM-IV classification are not always specific for the disorder. Therefore, epidemiological studies produce high rates of comorbid psychiatric conditions, especially if subjects are monitored longitudinally rather than cross-sectionally (lifetime or 12-month prevalence vs. point prevalence). These are consequences of criteria-based classification that need to be accounted for in selecting subjects for research and treatment.

Subjects with a primary anxiety disorder may develop a secondary depression, causing them to seek treatment. Treating the depression uncovers the underlying primary disorder. Anxiety subjects may also self-medicate with alcohol and other substances that are anxiolytic and be diagnosed with a substance use disorder. A patient with schizophrenia may develop a depression, and unless that is properly diagnosed the antipsychotic medication may be unnecessarily increased. A patient with recurring depressive episodes may eventually develop a manic episode, thus altering the diagnosis from unipolar depression to bipolar disorder. Subjects with substance use disorders may develop psychotic reactions to e.g., cannabis or amphetamine that may mimic schizophrenia. Since subjects with schizophrenia tend to seek various drug effects, the effects of cannabis or alcohol may cause psychiatric symptoms per se. There are many more instances of comorbidity that need to be understood.

Personality disorders

An issue with the DSM-IV classification is the distinction between axis I disorders and axis II personality disorders. Personality, cognitive style, and social attitudes are moderately or highly heritable according to adoption and twin studies. There is even a genetic contribution to being religious or antisocial, and to the amount of time spent watching television! Personality traits are stable and genetically determined throughout life, and are modifiable only by serious effects such as a neurodegenerative disease, severe substance use, a traumatic

brain injury, a brain tumor, or a severe generalized medical condition. One such famous case is Phineas Gage, a railroad worker who survived an iron rod that passed through his frontal lobes in 1848 and caused a pronounced personality change.

There have been many theories since Hippocrates to explain how personalities are shaped. The current explanatory model is the 5-factor model. That decribes a person along 5 different dimensions, e.g., being curious or rigid, dependable or careless, as well as degrees of self-confidence, stubbornness, shyness, and extrovertness. In the DSM-IV classification, personality disorders are assessed categorically, based on clinical assessments of cognition, affectivity, interpersonal functioning, and impulse control. If a person exhibits stable traits that deviate from the norms of the subject's ethnic group, they may be deemed a personality disorder. There are 11 DSM-IV personality disorders divided into 3 clusters. Personality disorders occur in about 10 per cent of population samples, and in about a third of clinical samples.

The distinction between axis 1 and axis 2 disorders is sometimes unclear. A patient with a serious axis I disorder may qualify for a personality disorder diagnosis, e.g., long-standing social anxiety disorder may be regarded as a phobic personality disorder if sufficiently impaired. Yet, such a patient may respond well to treatment. A subject with high-functioning autism or Asperger syndrome may be regarded as having a schizotypal personality disorder. Attention Deficit Hyperactivity Disorder (ADHD) may be confused with antisocial personality disorder. In the work groups for the DSM-V, these issues may cause a fundamental change in dealing with axis II personality disorders.

Somatic comorbidity

Somatic disease may cause or aggravate psychiatric disorders. For example, a patient with diabetes mellitus who has taken too much insulin may present confused or agitated in the emergency room because his blood sugar is too low. A patient with hypothyroidism or hyperthyroidism or hyperparathyroidism usually has anxious or depressive symptoms. Patients with acute intermittent porphyria may become psychotic, and are always anxious. Depression is known as a risk factor for acute myocardial infarction, and can add to the risk of cardiovascular complications. Patients with stroke often develop anxiety and depression. Such manifestations of somatic disease are important to recognize, and they are diagnosed on axis III in the DSM-IV.

Premenstrual dysphoria is an intermittent cluster of symptoms among which irritability and dysphoria are the most disturbing. It develops following ovulation and reaches a peak until menstruation occurs, obviously governed by hormonal variations across the menstrual cycle.

Multiple sclerosis can present with psychotic symptoms and mood elevations including euphoria. Wilson's disease is a disorder of copper metabolism that can cause rapid mood swings and cognitive dysfunction. Systemic lupus (SLE) can present with confusion and psychotic symptoms. Pernicious anemia (deficiency of vitamin B12) may present with depressive symptoms, memory deficits and sometimes confusion.

The medical model – is it useful?

The scientific community assumes that there is a molecular basis for psychopathology, and that symptoms are produced that can be elicited, quantified and classified by interviewing and observing a subject. This medical model was critiqued in the 1950s and 1960s, causing thought leaders to argue for external causation rather than disorders of the brain. Psychiatry was also abused for political purposes. Sane political dissidents in the Sovjet Union were sentenced by courts to be diagnosed and incarcerated in mental asylums and given tranquilizers (for some this may have been a better alternative than imprisonment).

Early support for the medical model came from twin studies that showed a strong genetic contribution to schizophrenia and bipolar disorder. Neurosyphilis, first defined in 1672, and thought to be an immoral disease, was determined to be an infectious disease in 1913. The Austrian psychiatrist Julius Wagner-Jauregg was awarded the Nobel Prize in 1927 for having shown that neurosyphilis could be treated by infecting the patient with malaria, and in 1943 patients began treatment with penicillin. The dramatic effects of lithium on mania were elucidated in the 1950s. The equally dramatic effect of chlorpromazine on delusions and hallucinations in schizophrenia was also discovered in the 1950s. With regard to anxiety, a break-through in 1964 was the finding by Donald F. Klein that imipramine could extinguish panic attacks, previously believed to stem from unconscious parental conflicts.

In recent years, the medical model has gained support from neuroimaging studies. The model has proven useful in that the benefits and hazards of psychotherapies and psychotropic medications have been shown in randomized controlled trials for which subjects with these diagnoses have been selected. The regulatory bodies of the world base their research protocols and marketing approvals on the ICD-10 and DSM-IV nosologies. Good Clinical Practice, the code by which treatment studies are undertaken, assumes that subjects are selected based on structured diagnostic interviews and that validated measures of changes in symptoms and functioning are applied (see below). The courts pronounce verdicts on forensic psychiatric assessments that are based on the medical model. The medical model is the basis for clinical research into the genetics, etiology, pathogenesis, epidemiology, treatments, and outcomes of psychiatric disorders.

The medical model is often poorly understood by lay persons in politics, administration and the media. It is attacked by the scientology movement and other antipsychiatric movements that refuse to acknowledge the scientific basis for psychiatric disorders. No wonder that the public is so confused, and that stigma against psychiatric disorders is so prevalent in many societies. Traditional medicine This paragraph is a brief excursion into the domain of traditional medicine and how it relates to psychiatric diagnoses. Examples of this interface are given.

The overwhelming majority of the world population will primarily be diagnosed and treated in traditional medicine that was developed locally by indigenous peoples:

Traditional medicine is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. (World Health Organization, 2000).

Complementary and Alternative Medicine (CAM) are recently developed therapies, often in opposition to evidence-based medicine:

... a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health systems of a particular society or culture in a given historical period (The Cochrane Collaboration, 2000).

There are approximately 500 000 certified practitioners of Traditional Chinese Medicine (TCM) in China, and additionally folk herbalists and "magic witch doctors," serving 56 ethnic nationalities with widely differing beliefs about illness causation, and with much stigma toward psychiatric disorders. While patients with obviously disorganized behavior will be admitted to psychiatric hospitals, those with lesser morbidities are primarily dealt with in TCM. Diagnoses are flexible from one day to another, and based on listening, observing, questioning, and pulse-taking. Religious healers, although forbidden, may apply fortune-telling, handwriting analysis, and palm-reading. They try to counteract evil spirits and repair relationships with ancestors. There is a Chinese Classification of Mental Disorders (CCMD-3) written in Chinese and in English in 2001, that includes about 40 ethnic diagnoses. One is shenjing shuairuo which emphasizes somatic complaints and fatigue, as in the ICD diagnosis neuroasthenia. Another is koro (an excessive fear of genitals and breasts shrinking back into the body).

At healing shrines in India, e.g., at the temples of Balaji in Rajasthan, most subjects have a diagnosable psychiatric illness including psychosis and severe depressive episodes. Healers name it spirit illness, and prescribe offerings and rituals at the temple and at home.

In Japan, Morita therapy was devised by a psychiatrist, and draws from Zen Buddhism, aiming to make people accept their destiny, and live with the symptoms that are similar to social anxiety disorder in the DSM-IV. There is a period of absolute rest, then a period of light work, followed by a period of normal work. In studies more than one half of all patients, including those with schizophrenia, had seen a traditional healer or shaman (yuta) before seeking psychiatric treatment. Taijin Kyofosho (anthropophobia, phobia of eye contact) is a culture-bound syndrome, rooted in consideration for others, loyalty to the group, protecting a vertical society, mutual dependence, a sense of obligation, and empathy.

In the Xhosa tribe in South Africa, amafufuynana and ukuthwasa are culture-bound syndromes that overlap with the DSM-IV criteria for schizophrenia. Both include delusions, hallucinations, and bizarre behaviour. A young person with ukuthwasa is a candidate to become a traditional healer, as he/she can communicate with ancestors, and resisting such a calling may cause illness. There is often a family history of schizophrenia and other psychiatric disorders among those with ukuthwasa. Amafufuynana is believed to be caused by sorcery.

In Quichuas, an Amerindian nation in South America, someone who suffers from anxiety or depression according to the DSM classification is diagnosed as the victim of sorcery or bad spirits.

In the United Kingdom, South Asian patients, including Muslims from Pakistan, frequently seek traditional healers (hakims), practicing Unani Tibbia that stems from Jundishapur south of Teheran. Psychiatric disorders are treated with herbs, diets, and amulets with holy words from the Koran, or the patient is referred to a mullah. Such treatments are

often conducted in tandem with biomedical treatments. African-Caribbean patients employ counter-measures including religious rituals and magic (Obeah - witchcraft), having consulted divine healers from the Pentecostal or other churches.

In Italy, the Catholic Charismatic Renewal, sanctioned by the Pope, stems from the Pentecostal cult and includes 300 000 believers. Illness, according to the Catholic doctrine of 2000, is closely related to Evil; it can be God's punishment for sins, and healing by God can be obtained by collective prayer that produces exalting salvation and jubilation.

These are some brief examples of the multitude of traditional explanations and treatments that are used for the large majority of the world's population. Traditional healers are a major force in global mental health, as about 40 per cent of their clients suffer from mental illnesses. A psychiatrist trained in evidence-based medicine thus needs to develop an understanding of the large influence of such faiths on patients with psychiatric disorders, even in technologically advanced societies, and need to adjust for it to establish a therapeutic alliance and improve the chances of a favorable outcome.

Structured diagnostic interviews and screening questionnaires

Many structured diagnostic interviews have been tested over the years. The first was the Present State Examination (PSE) in Great Britain in the 1950s that was integrated into the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, see below). The Mental Status Examination was developed in the United States in the 1960s.

Diagnostic interviews differ in scope and the qualifications of the interviewer, and in being based on ICD or DSM classification. Some are comprehensive and designed to find all psychiatric morbidity in general population samples, in primary care, or in tertiary care. Others deal primarily with e.g., affective disorders, substance use disorders, or personality disorders. Web-based case finding questionnaires are being developed to encourage people to seek treatment, as most individuals with conditions (such as substance use disorders, anxiety disorders, depression) amenable to treatment are not receiving any kind of treatment. Self-rating symptom scales are available for case-finding in e.g., the reception area of an outpatient unit, or to assess symptom changes in treatment studies.

Below are short descriptions of some currently used instruments.

The MINI Neuropsychiatric Interview was developed by David Sheehan and Yves Lecrubier as an efficient tool for the experienced mental health worker to look for 15 psychiatric diagnoses in an interview that takes about 30 minutes: Affective, anxiety, psychotic, substance use, eating, and antisocial personality disorders as well as current suicidality. The subject is instructed to simply answer yes or no to each question. Each section has one or a few lead-in questions, and in-depth questions in case there is a positive response. It is essential that the subject understands the questions, so the interviewer may have to repeat them or explain them. The questions are purposely overinclusive (false positives) so that cases will not be missed. It is critical that the interviewer has clinical judgment to assess the value of the subject's responses. Since somatic diseases may have caused the symptoms (such as a brain tumor, thyroid disease, or adverse effects of medications and substances), a physician must validate the interview results. An experienced nurse or psychologist or mental health worker may do the actual interview. The MINI is the most common interview in drug treatment

studies, and is available in over 40 languages. The English MINI version 6.0 was updated in 2009. It can be down-loaded without charge from www.medical-outcomes.com.

The Composite International Diagnostic Interview 3.0 (CIDI) is a fully structured non-clinical interview intended for use in general population surveys `http://www.hcp.med.harvard.edu/wmhcidi/instruments_download.php`.

The CIDI-SAM (SAM is for Substance Abuse Module) is a structured interview that ascertains DSM-III, DSM-III-R, Feighner, RDC and ICD-10 diagnoses for alcohol, tobacco and nine classes of psychoactive drugs. It was designed at the request of the World Health Organization to expand the substance abuse sections of the CIDI. The SAM module takes an average of 45 minutes to complete. `http://epi.wustl.edu/epi/assessments/SAM%20Info%20and%20Order%20Form.doc`

The Schedules for Clinical Assessments in Neuropsychiatry (SCAN) is a semi-structured clinical interview to assess major mental disorders `http://gdp.ggz.edu/scandocs/` in clinical settings.

Schedules for Affective Disorders and Schizophrenia (SADS) has been produced in several versions since 1975, and can take up to 3 hours to complete by a trained clinician. It is the basis for the Structured Clinical Interview for Diagnosis (SCID I and SCID II) that is also an expert instrument.

The Personality Diagnostic Questionnaire (PDQ-4) holds 99 true/false items to screen for 11 DSM-IV personality disorders `http://www.pdqtest.com/index.html`.

The General Health Questionnaire (GHQ-12) was developed in the 1970s for self-screening in primary care, public health surveys, and other settings with lower degrees of psychopathology. GHQ-12 asks if 12 symptoms have been present in recent weeks much more than usual, rather more than usual, no more than usual or not at all. Total scores derived using the Likert method (3-2-1-0) range from 36 to zero with higher scores denoting greater morbidity. It has proved reliable, stable and valid when tested in numerous primary care and hospital settings with a sensitivity and specificity versus CIDI of 79% and 77% respectively at cutpoint 11/12.

Another self-screen questionnaire is the Hospital Anxiety Depression Scale (HADS), developed in the UK to find cases with symptoms of anxiety and depression. It consists of 14 items that a subject can respond to within a few minutes, for example prior to a physician visit.

The Clinical Interview Schedule (CIS) was developed to assess anxiety, depression and somatization. The revised version (CIS-R) has been used in population surveys by lay interviewers.

The Kessler Psychological Distress Scale (K-10) checks if 10 mental symptoms have been present in the last 4 weeks for all, most, some, a little or none of the time. It was designed for use in general health surveys and has proved reliable and valid in surveys in the United States and in Australia `http://www.nevdgp.org.au/files/programsupport/mentalhealth/K10_English%5B1%5D.pdf`.

Legal issues and psychiatric diagnoses

The courts in most societies take a diagnosis of a psychiatric disorder into account before passing sentence. Usually the court will order that a subject undergoes a forensic psychiatric examination to determine whether there is a severe psychiatric disorder, and whether the subject can be held accountable for his actions. Does a subject with schizophrenia or antisocial personality disorder understand the consequences of his actions for other people and for society? Did the mother kill her child because of a depression, or because she was under the influence of auditory hallucinations? If there is an indisputable organic brain disease is the subject to be held accountable for a crime? These are evaluations that require an experienced, professional, thorough and highly regulated psychiatric assessment. The law varies between nations, and the court may order commitment to psychiatric care, or a prison term or both.

In many societies doctors are responsible by law to report if a patient is deemed unfit to possess a fire arm, or unfit to have a driver's license, or to have custody of a child. Such reports require a careful psychiatric diagnosis.

Medical records

In most countries, the history and mental health status examination should result in a clinical evaluation of the patient and at least one psychiatric diagnosis, all of which make up the core of the patient's medical record (chart). This may be a preliminary or definite diagnosis. For example, a patient presenting with typical symptoms of schizophrenia can be given a preliminary diagnosis that is confirmed after 6 months, because of the duration criterion in DSM-IV.

The physician can be held accountable to a disciplinary board if the diagnostic procedure is not properly recorded. The diagnosis is the basis for justifying treatments and perhaps involuntary care.

Records are still written by hand or typed in many countries. Increasingly in Europe and in the United States there is a move to electronic medical records. This is in the interest of administrators and regulators to hold physicians accountable and to increase patient safety. Insurers have a stake in psychiatric diagnoses to assess the risk of a potential subject for a health insurance or retirement plan. If records contain valid and reliable information about the patient's diagnosis, treatments, suicidal risk, and risk for aggression it will increase the quality of care. If all of the patient's health care contacts (the emergency room, primary care unit, psychiatric clinic) are eligible to read the patient's record it will increase patient safety, and reduce unnecessary investigatory procedures. There are opportunities for longitudinal case studies, research, and allocation of health care resources.

The potential drawback with a unifying electronic medical record is that it will be at the expense of person integrity and privacy. Particularly, a psychiatric record will contain highly sensitive information that should not be accessible to insurers and employers. Patients should have the option to decline such a unifying medical record that can otherwise be read by all eligible users of a computerized record system.

Suggested reading

Anne Farmer, Peter McGuffin, Julie Williams. Measuring Psychopathology. Oxford University Press 2002.

Samuel B. Guze. Why Psychiatry is a Branch of Medicine. Oxford University Press, 1992.

Mario Incayawar, Ronald Wintrob, Lise Bouchard, Goffredo Bartocci (eds.). Psychiatrists and Traditional Healers. Unwitting Partners in Global Mental Health. Wiley-Blackwell, 2009.

Donald W. Goodwin, Samuel B. Guze. Psychiatric Diagnosis - 4th Edition. Oxford University Press, 1989.

2 Psychotic Disorders

Schizophrenia and Related Psychotic Disorders

2.1 Introduction

Psychosis, a syndrome with many causes, traditionally refers to an impaired ability to distinguish between false and real perceptions and beliefs. Schizophrenia is the prototypical psychotic disorder. The most common psychotic symptoms are *positive symptoms* such as abnormal perceptions (including illusions and hallucinations), false beliefs, including a wide variety of delusional thoughts (e.g., paranoid delusions, delusions of reference, grandiose, somatic, etc.), and disorganized thinking. In addition, patients with schizophrenia might have prominent *negative symptoms* such as affective flattening, alogia (decreased thought/speech production), and avolition, together with amotivation, anhedonia and social isolation. Disorganized or bizarre behavior is a separate symptom dimension of the disorder. Affective symptoms can also be present and cognitive and social deficits are common.

This chapter focuses on primary psychotic disorders, as illustrated by schizophrenia, meaning that the clinical picture of psychosis is not deemed to be secondary to other processes. It is important to note that in addition to the primary psychoses a number of psychiatric and somatic conditions affecting the brain homeostasis can produce psychotic symptoms.

Patients with personality disorders (PDs) can present with overt psychotic symptoms in response to stress (e.g., paranoid PD, schizotypal PD, borderline PD). Schizoid PD is considered a risk factor and might precede Schizophrenia and Delusional Disorder. With regards to mood disorders, severe psychotic depression can present with mood congruent (e.g., nihilistic delusions, delusional guilt) and/or auditory hallucinations making critical and negative comments. At the opposite end of the spectrum, severe mania can present with grandiose and religious delusions, delusions of special powers, and auditory hallucinations (God's or angelic voices). Late life psychosis can be present in the later stages of dementia disorders. Conditions that affect the brain structure, either acutely [e.g., rapidly growing brain tumors, traumatic brain injury, strokes, infectious/inflammatory processes such as tertiary syphilis, multiple sclerosis or systemic lupus erythematosus (SLE)], or chronically [e.g., nutrient and vitamin deficiencies such as B12, niacin deficiency (pellagra), etc.] can present with a variety of psychotic symptoms. Last but not least, a number of drugs (prescribed and illicit) can be associated with psychotic symptoms either during treatment/intoxication or withdrawal.

This chapter will first review the definitions of the different types of psychotic symptoms, as the basis for the discussion about the approach (including initial assessment as well as short and long-term treatment plans) to a patient with a generic psychotic syndrome. For the remainder of the chapter schizophrenia is used as the foundation for the discussion of

clinical diagnosis, differential diagnosis, epidemiology, pathophysiology, genetics and treatment. Pertinent details of schizophrenia-related disorders will be discussed (compared and contrasted whenever the case) within the confines of the broader schizophrenia mainframe.

2.2 Clinical Manifestations and Definition of Terms

- **Positive Symptoms** are thought of as an excess of normal function. Overvalued misperceptions that become illusions and hallucinations and overvalued ideas that become delusions (fixed ideas) are classical examples of positive symptoms.
- **Negative Symptoms** refer to a lack of what is considered to be normal function. Normally, a degree of volitional ability is expected; therefore decreased or absent volition (avolition) is a negative symptom. Similarly, a lack of motivation (amotivation), a lack of ability to enjoy things (anhedonia), or decreased ability to engage in social activities (social isolation) are other classical negative symptoms.
- **Catatonia** refers to two extreme (and fundamentally opposite) states. Agitated catatonia refers to a state of excessive, extreme behavioral agitation (not in response to internal stimuli), while catatonic immobility refers to extreme negativism (the patient actively resists any attempts to have his extremities or whole body moved) or catalepsy (waxy flexibility). Other catatonic symptoms include posturing (assuming strange body postures), grimacing, mannerisms, stereotyped movements, echolalia (where the patient repeats in parrot-like fashion the words of another person), and echopraxia (where the patient imitates in mirror-like fashion the movements of another person).
- **Disorganized thinking** (**formal thought disorder**) refers to an alteration in the thought process. Normally the flow of thinking is coherent, linear and goal directed. In psychotic patients the associations may be loose to the point of being non-existent. The psychotic patient's thought form may present with tangentiality (ideas are only marginally connected) or circumstantiality (the patient responds to questions moving in gradually more focused, concentric circles until eventually reaching the answer). In extreme cases, even the structure of the sentence might be lost which results in word salad.
- **Disorganized behavior** refers to the patient difficulty to complete most goal oriented activities. A range of behaviors have been described: actively responding to inner stimuli (e.g., talking to oneself or shouting for no apparent reason), aimless, repetitive movements and activities, poor ability to maintain one's basic hygiene and perform routine actives of daily living (which often results in a disheveled appearance, and poor grooming and hygiene), or uncensored public sexual activity (being naked, or masturbating in public).
- **Active phase** refers to a period of time when a combination of the above symptoms are prominently manifested.
- **Prodromal** and **residual** phases refer to periods of time of attenuated symptoms that either precede (prodromal) or follow (residual) the active phase period.
- **Cognitive Symptoms**: Memory (more specifically working memory), attention, concentration, processing speed, problem solving (executive functioning), and social cognition are a few of the many cognitive domains shown to be impaired in schizophrenia.

- **Insight** is a multidimensional concept referring to awareness of illness, specific symptoms and their consequences, as well as need for treatment. Insight refers to the patient's ability to understand that some of his or her non-reality based experiences (usually hallucinatory experiences and delusional representations) are secondary to having schizophrenia rather than reality. Awareness and attribution of both current and past symptoms represent specific aspects of insight. Additional dimensions of insight include a more global understanding of the diagnosis and need for treatment.

2.2.1 Approach to the Patient with Acute Psychosis

The following major issues should be kept in the forefront:

1. What is the most accurate diagnosis?
2. Is there a treatable or reversible component to the psychosis?
3. Is the patient safe?
4. Can the physician help to alleviate the positive symptoms?
5. Can the physician help to alleviate the negative, cognitive symptoms and insight deficits to improve social/functional outcomes?

2.2.2 History

The history should clarify the onset (acute versus gradual), tempo (slow/protracted versus rapid), chronology, course (persistent versus episodic), and type of symptoms.

Onset and tempo

An acute or subacute onset of psychosis may represent delirium, psychosis due to a general medical condition, or a substance induced psychosis and should trigger the search for intoxication, infection, or metabolic derangement.

Duration

According to the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) a diagnosis of schizophrenia requires the presence of a combination of prominent positive, negative, disorganized thinking (formal thought disorder), catatonia, or behavior type of symptoms for at least a month (active phase), with a total duration of the episode (including active phase, and some type of prodromal or residual symptoms) for at least 6 months and resulting in social and occupational dysfunction.

A schizophrenia-like presentation that lasts more than a month but less than 6 months would be more appropriately diagnosed as **schizophreniform disorder**. **Brief psychotic disorder** should be diagnosed when the total duration of symptoms is shorter than a month. **Schizoaffective disorder** trumps schizophrenia if in addition to stand alone episodes of psychotic symptoms there is also a long history of affective symptoms, and the affective symptoms occurred for a longer time than the psychotic symptoms.

Chronology

Refers to the temporal rapport between the different symptoms. Clarifying what started and what followed are essential in ruling out phenomenologically overlapping disorders. If it is

determined that the psychotic symptoms *followed* a medical condition or drug (prescribed or illicit) **psychotic disorder due to a general medical condition**, **substance induced psychotic disorder**, or **delirium** need to be considered first. **Mood disorder with psychotic symptoms** is diagnosed if the history shows that psychotic symptoms *always occurred* in the context of already present, and most often severe affective (depressive and manic) symptoms.

Course

A clearly episodic course is most times indicative of a primary affective disorder. Unfortunately, schizophrenia tends to be chronic, with some level of residual symptoms following the active phase for most patients. However, for schizophrenia, after one year since the onset of the acute phase symptoms, DSM allows for a number of course based specifiers including: single episode with partial/total remission, episodic with/without inter-episode residual symptoms, and continuous.

2.2.3 Physical and Neurological Examination

A thorough general and neurological examination is recommended.

General physical examination

Is recommended to first rule out a systemic disease that may be responsible for the psychotic syndrome. A number of non-specific physical abnormalities including an arched palate, narrow or wide–set eyes or subtle ear malformations are more frequently reported in patients with schizophrenia than in the general population. For patients treated with antipsychotics a physical exam will document the general state of health and is important to exclude side effects of medication. Side effects include orthostatic hypotension, hypersalivaton (secondary to clozapine), anticholinergic syndrome (dry mouth, and tachycardia secondary to anticholinergics), hyperprolactinemia (lactation secondary to D2 antagonism), and metabolic syndrome (most common with clozapine and olanzapine).

Neurological examination

Is recommended to rule out neurological conditions that may present with psychotic manifestations; of note, abnormal focal neurological signs are not typically found in primary psychotic disorders. Such findings should prompt the clinician to do a more extensive neurological work-up. In addition, a neurological exam is necessary to exclude the presence of *soft neurological signs* and *abnormal involuntary movements. Soft (neurological) signs*, while not pathognomonic, are frequently seen in schizophrenia, where "soft" denotes the absence of a clearly localized ("hard") central nervous pathology that can explain the observed deficits. They include:

- Sensory function integration abnormalities include poor audio—visual integration, astereognosis (the inability to identify an object by touch without visual input), and agraphaesthesia (the inability to recognize writing on the skin purely by the sensation of touch).
- Motor function integration abnormalities might include balance and gait abnormalities, poor coordination, intention tremor, finger—thumb opposition difficulties.

In addition, a number of abnormal involuntary movements have been classically described in chronic schizophrenia (before the neuroleptic age) but have been much more prevalent since the introduction of antipsychotic dopamine antagonist drugs. These include:

- *Akathisia*, which refers to low amplitude, high frequency movement typically involving the lower extremities. The patient reports a feeling of intolerable restlessness, specifically manifested as a need to continuously move one's feet. The patient cannot stop pacing (paces in place when asked to sit or stand without walking),
- *Dystonia*, which refers to a high amplitude, low frequency, spastic type of movement, typically involving an isolated muscle group, e.g., oculopharogyric crisis (eyes turned upwards), torticollis (neck turned sideways), laryngeal spasm (rare but serious as it might result in asphyxia), opisthotonus (arched back, rare, painful)
- *Dyskinesia*, which refers to low amplitude, repetitive, moderate frequency, pseudo-parkinsonian movements that may involve any muscle group but most typically involve the fingers, hands, toes, feet, lips and lower face muscles (including perioral and mandibular muscles)
- *Tremor*, which refers to a low amplitude, high frequency, repetitive movement. Tremor of the hands and fingers can be spontaneous or can be elicited by asking the patient to put his arms in a horizontal position and stretch his fingers. In addition, a parkinsonian pill rolling tremor may also be observed. In patients taking lithium a fine tremor(very low amplitude, very high frequency) may be seen.

2.2.4 Mental Status Examination (MSE)

- **Appearance:** disheveled or bizarre appearance may be a clue to underlying psychosis. Impaired reality testing commonly results in poor grooming and hygiene.
- **Attitude:** paranoid patients may be unwilling to co-operate during an interview, while very psychotic patients my be unable to engage with the interviewer.
- **Motor behavior:** posturing, repetitive gestures, extreme psychomotor agitation (without any apparent precipitants or retardation) can indicate a catatonic presentation. Alternatively, the patient may present with psychomotor agitation in response to overwhelming internal stimuli (e.g., loud, demeaning voices or threatening visions) or because of severe paranoid ideation.
- **Mood:** patient's reported mood can vary from good to depressed or afraid.
- **Affect:** paranoid patients present with guarded affect, eyes scanning the room, and a closed up body language.
- **Speech/thought process:** can be vague, circumstantial or overtly disorganized. At times nonsensical neologisms, word salad, clang (rhyming, nonsensical associations) are present.
- **Thought content:** may be positive for delusional ideation (most common ideas of references and paranoid delusions). In addition, the patient may harbor suicidal and violent thoughts due to his persistent psychotic symptoms or, at times, related to concomitant depressive symptoms.
- **Perceptual disturbances:** auditory hallucinations can be commanding and order the patient to kill himself or other people. When visual hallucinations are present they tend to be unpleasant as a rule and are often overtly terrifying.

- **Insight and Judgement:** judgement is mostly impaired and the patient has very limited, if any, insight.
- **Cognition:** with the possible exception of decreased attention, other cognitive deficits may not be obvious during a cursory MSE.

2.2.5 Cognitive Examination

In schizophrenia neuropsychological testing routinely reveals deficits in working memory, executive functioning, social functioning, processing speed, verbal fluency, and/or reaction time abnormalities. Unfortunately, the ability to test for these deficits routinely in clinical practice is limited by the lack of good, time efficient screening cognitive instruments for schizophrenia and related disorders.

2.2.6 Laboratory Tests

There are no tests that can rule in a diagnosis of schizophrenia or related disorders. The role of laboratory investigations are to rule out substance induced disorders and general medical conditions that can present with a psychotic syndrome; to establish a baseline and monitor physiological functions that can be affected by, or can affect the metabolism of psychotropic medications; and monitor drug levels when necessary.

Investigations to exclude a substance induced disorder or general medical condition:

- urine[1] or blood toxicology screen: should be performed routinely in all patients presenting with new onset or exacerbated psychotic symptoms, as a number of illicit drugs can cause/worsen psychosis (e.g., hallucinogens, cocaine, stimulants, marijuana).
- Complete blood cell count[2] (CBC): blood dyscrasias can point to an underlying vitamin deficit that may manifest with psychosis (e.g., pernicious or megaloblastic anaemia as a sign of vitamin B12/folate deficits)
- Rapid plasma reagin[3] (RPR): done to rule out (tertiary) syphilis
- Thyroid panel[4]: indicated when there is a clinical suspicion for hypo or hyperthyroidism
- Brain Imaging:
  - Structural brain imaging (CT or MRI) is indicated to rule out other brain pathologies (e.g., multiple strokes, demyelination, masses). Neuroimaging studies do not show a pattern of findings specific for schizophrenia or related disorders and may be normal early in the course of the disease. As schizophrenia progresses, enlarged ventricles and diffuse cortical atrophy becomes apparent. MRI scans may also show atrophy of the parahippocampal gyrus, dorsolateral prefrontal cortex, mesolimbic system, the anterior cingulate cortex, and planum temporalis asymmetry reversal or generalized reductions in grey and white matter.

1 http://www.labtestsonline.org/understanding/analytes/drug_abuse/test.html
2 http://www.labtestsonline.org/understanding/analytes/cbc/test.html
3 http://www.labtestsonline.org/understanding/analytes/syphilis/test.html
4 http://www.labtestsonline.org/understanding/analytes/thyroid_panel/glance.html

- Functional brain imaging studies (PET and functional MRI) demonstrate abnormalities in the same regions. However, none of these changes are pathognomonic for schizophrenia or related disorders.

A liver function panel and chemistry panel (to document renal function) are recommended to establish a baseline for physiological functions that can affect the metabolism of psychotropic medications. Other tests that may be indicated to monitor side effects of psychotropic medication include a blood glucose level, a lipid panel, and an ECG (as some antipsychotics have the potential of prolonging the QTc interval). A prolactin level should only be measured when prolactinemia is suspected on clinical grounds.

The following drug levels need monitoring: lithium (0.7 to 1.2 mEq/L), carbamazepine (5 to 12 mcg/mL), and valproic acid (50 to 100 mcg/mL). A clozapine level above 350 ng/mL is recommended to establish compliance and has been shown to correlate with improved efficacy for refractory schizophrenia. There is no clear evidence of a therapeutic range for other antipsychotics.

2.3 Specific Types of Primary Psychotic Disorders

2.3.1 General Considerations and Differential Diagnosis

When a patient presents with a psychotic syndrome the first order of business is to establish if the presenting symptoms are due to another psychiatric or somatic condition. In other words, a psychotic syndrome is classified as "primary psychosis" only after other possible underlying pathologies have been ruled out.

In terms of somatic contributors, the main suspects should include processes that may affect the brain either acutely or chronically, in which case a diagnosis of psychotic disorder due to a general medical condition is appropriate. A substance induced psychotic disorder should be diagnosed if there is a likely cause and effect relationship between a substance (including medication, OTC products or illicit drugs) and the psychotic presentation. Psychiatric underlying pathologies include severe depressive and bipolar disorder, which may present with mood congruent psychotic features. As discussed, under stress, some personality disorders may present with transient psychotic symptoms.

The differential diagnosis between different primary psychotic disorders should take into account the type and duration of symptoms. Virtually identical symptoms are seen in schizophrenia, brief psychotic disorder, and schizophreniform disorder. The symptom duration differentiates brief psychotic disorder (1 day to <1 month) from schizophreniform disorder (1 month <6 months) and schizophrenia (>6 months). Delusional disorder is differentiated from schizophrenia based on prominent, non-bizarre delusions without any other associated symptoms. When distinct psychotic episodes are present but affective symptoms account for the majority of the clinical presentation a diagnosis of schizoaffective disorder should be considered.

2.4 Schizophrenia

2.4.1 Conceptual History and Diagnostic Classification

- 1853: Morel's curious cases of *Démence Précoce*: Bénédict Morel[5] introduces the concept of *Démence Précoce*, literally "early dementia", described a distinct syndrome affecting teenagers and young adults. The syndrome is characterized by bizarre behavior and mental function, withdrawal and self neglect starting in adolescence.
- 1868: Kahlbaum's *Katatonie*: Karl Ludwig Kahlbaum[6] and Ewald Hecker[7] publish *Die Gruppierung der psychischen Krankheiten* (The Classification of Psychiatric Diseases). By considering the longitudinal course of psychiatric symptoms in addition to the clinical presentation Kahlbaum and Hecker were the first to describe and name a number of psychiatric syndromes including *cyclothymia*, *dysthymia*, *paranoia*, *catatonia*, and *hebephrenia*. Kahlbaum's *Katatonie* was characterized by stereotyped movements, outbursts of excitement and stupor.
- 1870: Ewald Hecker's *hebephrenia* and *cyclothymia*: Hecker differentiates between *hebephrenia*, a disorder that begins in adolescence with erratic behavior followed by a rapid decline of all mental functions, and *cyclothymia*, a cyclical mood disorder.
- 1891: Arnold Pick[8] reports on a case of a psychotic disorder which he calls *Dementia Praecox*
- 1893: Emil Kraepelin's[9] *Dementia Praecox*: Kraepelin new classification of mental disorders distinguishes between *dementia praecox* and mood disorder (termed manic depression and including both unipolar and bipolar depression).
  - *Dementia Praecox*: A "sub-acute development of a peculiar simple condition of mental weakness occurring at a youthful age."
  - Distinct from *catatonia* and *dementia paranoides*.
  - Kraepelin's concept relied heavily on course (chronic versus episodic) and prognosis
- 1899: *hebefrenia*, *catatonia* and *dementia paranoides* as subtypes of *dementia praecox*.
- 1919: Kraepelin writes that "it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect."
- 1908: Eugen Bleuler[10]'s *Schizophrenia* gk. skhizein "to split"+ phren (gen. phrenos) "diaphragm, heart, mind", where "split mind" referred to being split off from reality and unable to distinguish what is real from what is not real. Of note, Bleuler never implied that people with schizophrenia have split personalities; he proposed the term of schizophrenia to describe the separation of function between personality, thinking, memory, and perception.
  - Bleuler 4 A's: flattened Affect, Autism, impaired Association of ideas and Ambivalence.

5 http://en.wikipedia.org/wiki/B%C3%A9n%C3%A9dict_Morel
6 http://en.wikipedia.org/wiki/Karl_Ludwig_Kahlbaum
7 http://en.wikipedia.org/wiki/Ewald_Hecker
8 http://en.wikipedia.org/wiki/Arnold_Pick
9 http://en.wikipedia.org/wiki/Emil_Kraepelin
10 http://www.answers.com/topic/eugene-bleuler

- Bleuler proposal for a new name also stemmed from his dissatisfaction with the implications of dementia praecox label. Bleuler noted that schizophrenia was NOT a dementia, as some of his patients improved.

- 1887 – 1967: Kurt Schneider[11] described the first rank symptoms (FRS), thought to be specific for schizophrenia psychosis. He included thought insertion/broadcast/withdrawal, made feelings/impulses/actions/somatic sensations (a type of delusion), third person auditory hallucinations (running commentary or arguments), delusional perception, and thought echo (*echo de la pensee* or *gendankenlautwerden*) – a type of hallucination. Only 58% of patients with a diagnosis of schizophrenia experience at least one FRS, while 20% never experience FRS. Furthermore, 10% of patients with a diagnosis of schizophrenia experience FRS.

- Modern positive and negative symptoms based classification systems:

  - **Positive** symptoms include distortions or excesses of normal functioning such as, hallucinations, delusions, disorganized thinking and speech, and inappropriate affect. Frequently hallucinations are auditory in nature; rarely they may be visual, tactile or olfactory. Delusions are fixed false beliefs held despite negative evidence, and are not consistent with cultural norms. Types include persecutory, referential, somatic, grandiose, etc. Positive symptoms are generally more responsive to treatment than negative symptoms.
  - **Negative** symptoms involve a decrease or absence of normal behavior. They include affective flattening, impoverishment of speech and language, avolition, amotivation, lack of interest, anhedonia, and social isolation.

- Modern classifications:

  - Andreasen's Positive and Negative Symptoms Type
  - Crow Type I and II:

    - Type I – positive symptoms, good response to treatment, relatively better outcome
    - Type II – negative symptoms, poorer response to treatment, relatively poor outcome, MRI changes.

2.4.2 Current classification – ICD 10/ DSM-IV-TR

Common ICD/DSM types:[12]

- *Paranoid* schizophrenia:

  - Prominent delusions, auditory hallucinations
  - Usually minimal thought disorder or negative symptoms

- *Catatonic* schizophrenia is characterized by prominent psychomotor symptoms e.g., violent excitement, posturing, waxy flexibility, automatic obedience, perseveration, stupor.
- *Residual* schizophrenia or "defect state", when positive symptoms give way to negative symptoms.

11 `http://en.wikipedia.org/wiki/Kurt_Schneider`

12 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

- *Simple* schizophrenia refers to insidious development of negative symptoms without positive symptoms

DSM IV only:[13]

- *Disorganized* schizophrenia: mainly thought disorder, and negative symptoms, without prominent positive or affective symptoms.

ICD 10 only:

- *Hebephrenic* schizophrenia: affective abnormality, thought disorder, mannerisms. May have chronic course.

2.4.3 Epidemiology and Risk Factors

The life time prevalence of schizophrenia is between 0.5-1.5% in the general population and is one of the ten leading causes of disability worldwide. Of note, this 1 in 100 rate has been shown to be remarkably constant across different historical periods and across different cultures. The annual incidence is reported to be in the range of 0.5 to 5 per 10,000. The onset of schizophrenia is usually between the ages of 20-45. Most times, the course of the disorder is chronic and characterized by a gradual, progressive deterioration. However partial or complete recovery is reported to occur for 30-60% of patients following a first episode of schizophrenia.* About 20-40% of patients with schizophrenia attempt suicide at least once during their lifetime, and about 10-15% die of suicide. The prevalence in males and females is equal.[14]

The following risk factors have been reported for schizophrenia:

- Men tend to be diagnosed earlier than women (males age 15-25 years, females age 25 – 35 years)
- Seasonality: winter birth excess
- Schizoid and schizotypal personality disorders
- A family history of schizophrenia or major affective disorders
- A family with a high level of expressed emotions (EE)
- Schizophrenia tends to be more frequent in urban areas and in developed countries
- Lower socioeconomic status
- Schizophrenia is more frequent in recent immigrants (deprivation, stress of immigration may increase risk)

2.4.4 Genetic Considerations

The rate of schizophrenia is increased in families with affected members. Mode of Transmission is unknown and likely to be multi-factorial, possibly polygenic. 70% of the heritability of schizophrenia is genetic. Adoption studies have shown an increased incidence of schizophrenia spectrum disorders among adopted offspring of schizophrenic parents. When one parent

13 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

14 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

has schizophrenia there is a twelve fold increase in the risk of developing the disorder; with one affected sibling there is a 9 fold increase in risk; for monozygotic, identical twins the rate of concordance is around 50%. Working memory appears to be heritable and showed significant associations with DISC1, reelin, and AKT1 in schizophrenia.

2.4.5 Pathology

While there are no structural or functional brain changes specific to schizophrenia or other psychotic disorders a number of abnormalities are reported. Enlarged ventricles, deep cortical sulci, diffuse gray and white matter loss, increased neuronal density, decreased synapse density, and an overall decrease in brain size have been reported in schizophrenia studies using structural brain imaging (CT, structural and diffusion sensor MRI studies) or postmortem observations. Smaller frontal and temporal lobes, lower volume hippocampus, thalamus, corpus callosum, and anterior cingulate, as well as larger caudate and putamen have been reported in schizophrenia.

Decreased activation in dorsolateral prefrontal cortex (during working memory task), and increased activation of the superior temporal gyrus (during auditory hallucinations) have been also reported in functional brain imaging (fMRI and PET) studies.

2.4.6 Etiopathological Theories

Neurodevelopmental Theories

Impaired fetal or neonatal brain development may sow the seeds for the onset of psychotic symptoms in later life. Patients with schizophrenia have a lower than average IQ, and often subtle/soft neurological signs. A number of parental risk factors have been reported including multiparity, maternal bleeding during pregnancy, small baby size for gestational age, increased paternal age, and severe stress to mother during first trimester. In addition, the following environmental risk factors have been associated with increased risk of developing psychotic illness later in life: late winter birth, prenatal exposure to famine, in-utero exposure to analgesics, and cannabis use.

Biological factors

Electrophysiology

- P50 sensory gating deficits: following an auditory stimulus schizophrenia patients fail to gate a subsequent stimulus that follows closely (within the normal 50 msec suppression).
- Reduced P300 evoked response potential (ERP) [oddball deficit paradigm]: schizophrenia patients fail to respond to an odd ball stimulus administered during a series of otherwise identical stimuli.
- Prepulse Inhibition (PPI) Paradigm.

Neurotransmitters

Dopamine (DA)

- Hypothesis: excessive DA activity in mesolimbic and cortical brain regions. Schizophrenia is the result of a dopaminergic hyper-salient state [15]
- Supporting evidence:
  - Postmortem studies: increase DA receptors in schizophrenia
  - HVA (dopamine metabolite) in plasma, CSF and severity of psychosis/response to neuroleptics
  - DA Agonists
    - Amphetamines release DA at synapses and cause positive symptoms (in people who do not have schizophrenia)
    - L-dopa increases central DA concentrations and causes positive symptoms
    - DA Antagonists: All effective antipsychotics are D2 receptor antagonists; efficacy correlates with D2 occupancy
- Limitations:
  - Amphetamines and L-dopa do not produce negative symptoms
  - Antipsychotics are ineffective in 30% of patients
  - Antipsychotics block D2 receptors instantly but antipsychotic effect not evident for days

Serotonin

- Hypothesis: serotonin excess
- LSD and psilocybin are potent 5HT receptor agonists and cause positive symptoms of schizophrenia (in people who do not have schizophrenia)
- Atypical antipsychotics are potent 5HT2 receptor antagonists
- Limitations: LSD produces visual hallucinations which are uncommon in schizophrenia

Excitatory amino acids (EAAs): glutamate and aspartate

- Hypothesis: EAAs deficit
- Phenylcyclidine (PCP), which antagonizes EAA receptors, can produce positive and negative symptoms in people without schizophrenia
- Glutamate agonists (e.g., glycine), may be modestly therapeutic in schizophrenia

Psychological Factors

- Freud: delusions as a way of making sense of a disturbed internal world ("I need to respond with aggression to protect myself as everyone is attacking me").
- Klein: failure to resolve the paranoid/schizoid position
- Cameron: loss of conceptual boundaries
- Goldstein: concrete thinking

15 Kapur S.Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia.Am J Psychiatry. 2003 Jan;160(1):13-23

- Difficulties in filtering sensory input (see also electrophysiological findings)

Familial/Social Factors

- Probably more important in precipitating schizophrenia than causing it
- Lidz's marital schism/marital skew
- Bateson's double bind theory
- High expressed emotion

Social Factors

- Social adversity in childhood and fetal life associated with risk of developing schizophrenia and other psychoses later in life
- Risk factors for psychoses later in life (in developed countries):
  - households receiving social welfare benefits
  - unemployment
  - single-parent households
  - low socioeconomic status
  - rented apartments[16]

2.4.7 Clinical Diagnosis

According to DSM-IV Schizophrenia is diagnosed when the patient presents with a combination of positive (delusions and hallucinations) and negative symptoms, which have been present for at least 6 months and have resulted in significant dysfunction. It is also accepted that disorganized speech/behavior and/or catatonic symptoms, when combined with other positive or negative symptoms, can count toward a diagnosis of schizophrenia. Schizophrenia is a diagnosis of exclusion; in other words, it is required that there are no other medical, psychiatric, or substance-induced conditions that would explain the patient's diagnosis better than schizophrenia.[17]

2.4.8 Differential Diagnosis

Early in the disease course, other etiologies of psychosis should be excluded. These include treatable conditions such as tertiary syphilis, vitamin deficiencies, brain tumor, drug and medication intoxication, chronic infection, and mood disorders. While neuroimaging studies (CT and MRI) do not show a single specific pattern with schizophrenia or related disorders and may be normal early in the course of the disease a screening CT is recommended for patients with a first episode of primary psychosis, especially for late or acute onsets. An affective psychosis (mania or depression with psychotic features) should be ruled out if

16 Wicks S, Hjern A, Gunnell D, et. Social adversity in childhood and the risk of developing psychosis: a national cohort study. Am J Psychiatry. 2005 Sep;162(9):1652-7

17 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

affective symptoms preceded psychotic symptoms or are dominating the clinical picture at the time of presentation. A diagnosis of schizoaffective disorder is appropriate if historically the course has been dominated by affective symptoms and there are at least some episodes of "pure" psychosis i.e., independent of the affective background. Symptom duration will separate brief psychotic disorder (<1 month), schizophereniform disorder (<6 months), and schizophrenia (>6 months).

2.4.9 Treatment

Hospitalization is recommended if the acute psychotic symptoms result in danger to self or others or significant impairment.

Biological

Traditionally, dopamine 2 (D2) antagonists (blockers), most often labelled as first generation (typical) neuroleptics, have been the pillar of schizophrenia treatment.

- D2 blockers, by decreasing the presumably excessive mesolimbic dopamine, have established efficacy for positive psychotic symptoms; however, due to concomitant blockade of the frontostriatal dopamine pathway, where dopamine is presumably decreased all along in schizophrenia, they do not improve (and in some cases can worsen) negative, cognitive symptoms, and/or functional/social outcomes.
- Due to an alteration of the physiological dopamine/acetylcholine ratio in the basal ganglia these drugs also have a number of extra-pyramidal adverse effects (EPSEs) both short term (acute dystonia, dyskinesia, akathisia) and long term (parkinsonism and tardive diskinesia).
- Finally, following a dopamine blockade in the tuberoinfundibular system, there is a prolactin increase with common sexual side effects, including decreased sexual interest, sexual difficulties, lactation and (in men) gynaecomastia.
- The side effects of typical neuroleptics can be stigmatizing and are a major reason for non-adherence to treatment.

Some of the above issues have been resolved with the advent of the second generation antipsychotics (SGA) or atypical neuroleptics, a drug class that tends to share the mechanism of D2 and 5HT2 (serotonin) antagonism. We say "tends to share" rather than "share the characteristic" as the second generation drugs show a number of differences in terms of both receptor profile and affinities. To illustrate, the prototypical atypical neuroleptic is clozapine, a drug that has strong D4 and 5HT2A antagonism but only partial D2 antagonism.

- SGAs have fewer EPSEs and tend to be better for negative symptoms than typicals (not increasing negative symptoms).
- Some of the atypicals (e.g., olanzapine, clozapine) increase the risk for metabolic adverse effects including significant weight gain, diabetes and dyslipidemia.
- Clozapine is recommended for treatment resistant schizophrenia.
- Generally SGAs, with the exception of olanzapine and clozapine, are first line treatments. This preference is based more on better tolerability (less EPSEs and cognitive adverse effects) than greater efficacy. On a case by case basis first generation antipsychotics

(FGAs) may represent a reasonable alternative.[18] Perphenazine and molindone efficacy and overall tolerability has been shown to be similar to SGAs.

General prescribing principles:

- Initial management may include use of sedative medication such as lorazepam.
- IM medication may be required in a very disturbed, involuntary patient.
- Depot (long-acting) neuroleptics are indicated when treatment adherence is problematic.
- Polypharmacy is common yet not supported by evidence.
- The goal of treatment is stability on monotherapy at the lowest effective dose.

Psychological (Individual and Family Interventions)

- Good evidence:
  - Education of patient and carers
  - Reduction of high expressed emotion: shown to affect relapse rates
  - Supportive, solution oriented psychotherapy
- Unclear benefit:
  - Cognitive behavioral therapy
  - Cognitive and functional rehabilitation
  - Self–help unclear

Social

- Good evidence:
  - Regular intensive case management
- Unclear benefit:
  - As needed case management
  - Consumer based organizations

2.4.10 Prognosis

15-25% of patients diagnosed with schizophrenia have one episode and no residual impairment. 25-40% have recurrent episodes and no residual impairment. 5-10% have recurrent episodes and develop significant non-progressive impairment. 30-40% have recurrent episodes and develop significant progressive impairment. Therefore, the majority of patients do not recover fully BUT DO NOT have a chronic unremitting course. There is little evidence that antipsychotics have altered the course of illness for most patients. However, evidence

18 APA Practice Guidelines Guideline Watch (September 2009): Practice Guideline for the Treatment of Patients With Schizophrenia.PsychiatryOnline.com Online ISBN 0-89042-336-9. Accessed 03/01/2011

suggests that prolonged psychosis which is untreated has a bad prognosis. Suicide rate is up to 15%.[19]

Good prognostic factors:

- Female gender
- Older age of onset
- Married
- Higher socioeconomic status
- Living in a developing (as opposed to developed) country
- Good premorbid personality
- No previous psych history
- Good education and employment record
- Acute onset, affective symptoms, good adherence to medication.

Predicting risk of suicide:

- Acute exacerbation of psychosis
- Depressive symptoms
- History of attempted suicide
- Male gender
- Command auditory hallucinations

2.5 Schizophreniform Disorder

Clinical Manifestations and Diagnosic Considerations

The clinical presentation is identical to schizophrenia, however impairment in function is not a requirement. The required duration of symptoms is of at least a month but less than 6 months. If symptoms persist for longer than 6 months it is appropriate to change the diagnosis to schizophrenia.[20] The diagnosis requires for other pathologies that may be responsible for the clinical manifestations (e.g., medical and drug use) to be ruled out before a diagnosis of schizophreniform disorder is made. It is not clear if schizophreniform disorder is a different disorder or just a more acute, better prognosis type of schizophrenia.

Subtypes/Specifiers

With good prognostic features:

- Good premorbid level of function
- Abrupt onset
- Confusion
- Absence of flat affect

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20 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

Without good prognostic features: when less than 2 of the above features are present[21]

Epidemiology

The prevalence is low overall. There may be differences between developed countries (estimated around 0.2%) and developing countries (estimated around 1%).[22]

Treatment Considerations

- Hospitalization is recommended if the acute psychotic symptoms result in danger to self or others or significant impairment.
- Acute psychosis should be treated with antipsychotics. Second generation antipsychotics, with the exception of olanzapine, are preferred first line.
- Treatment should be continued for one year and reassessed after.
- Supportive and solution oriented psychotherapy is beneficial.

Prognosis

About one third of the patients recover. The rest of the patients initially diagnosed with schizophreniform disorder progress to schizophrenia or schizoaffective disorder.[23]

2.6 Brief Psychotic Disorder

Clinical Manifestations and Diagnosic Considerations

Phenomenologically there is no difference between brief psychotic disorder (BPD), schizophreniform disorder, and schizophrenia. The difference between these three diagnoses is based on symptom duration. As indicated by its name, the duration of symptoms in BPD are brief: more than 1 day but less than 1 month. When the symptoms last longer than a month but less than 6 months the diagnosis changes to schizophreniform disorder. The psychotic symptoms should not be part of a pre-existing medical, drug induced, or primary psychiatric condition (including other psychotic or mood disorders).[24]

Subtypes/Specifiers

DSM-IV-TR specifiers include:

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22 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

23 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

24 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

- With marked stressor(s) (brief reactive psychosis)
- Without marked stressor(s)
- With postpartum onset: when onset of symptoms is within 4 weeks postpartum[25]

Epidemiology

Rare overall but more frequent in developing countries compared to developed countries.[26]

Treatment Considerations

Hospitalization is recommended if the acute psychotic symptoms result in danger to self or others or significant impairment. Neuroleptics for short term treatment should be considered on a case by case basis.

Prognosis

By definition full remission of symptoms and return to prior level of functioning is expected within a month.

2.7 Schizoaffective Disorder

Clinical Manifestations and Diagnostic Considerations

The patient presents with symptoms of schizophrenia, mania, depression or a combination of mood and psychotic symptoms. The history is significant for at least one distinct episode of psychosis not overlapping with mood symptoms and a relative temporal predominance of mood symptoms.

Differential diagnoses should include drug induced and medical conditions with secondary psychotic symptoms. While patients with schizophrenia can experience mood symptoms their duration is relatively short relative to the total duration of illness. When the psychotic symptoms represent a culmination of a severe mood episode a diagnosis of mood disorders (i.e., bipolar and major depression) with psychotic features should also be included in the differential. [27]

25 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

26 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

27 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

Epidemiology

Unclear but possibly less common than schizophrenia.[28]

Treatment Considerations

Hospitalization is recommended if the acute psychotic symptoms result in danger to self or others or significant impairment.

Antipsychotics are recommended for acute psychotic symptoms. Second generation antipsychotics (SGA), excluding olanzepine, should be considered as first line. Mood stabilizers including lithium, valproic acid, and carbamazepine, or SGA are recommended for acute manic symptoms. A neuroleptic-mood stabilizer combination may work better than either agent alone, and augmenting a neuroleptic with lithium or valproic acid should be considered as an augmentation strategy in cases of poor response to neuroleptic monotherapy. Antidepressants should be used conservatively for depressive symptoms. Close monitoring is required as an antidepressant can precipitate a manic switch in a patient with schizoaffective disorder.

Prognosis

Better than schizophrenia but not as good as mood disorders.[29]

2.8 Delusional Disorder

Clinical Manifestations and Diagnostic Considerations

The patient presents with non-bizarre delusional beliefs but most often the mental status examination is otherwise fairly normal. The delusional ideas are restricted to a specific subject and do not contaminate other mental processes. Other psychotic symptoms may include olfactory/gustatory hallucinations, which may be prominent and are closely related to the main delusional themes. If prominent auditory/visual hallucinations are present a diagnosis of schizophrenia rather than delusional disorder may be more appropriate. Associated symptoms are rare but may include mood or anxiety symptoms. When present, such symptoms are often secondary to the delusional beliefs (e.g., "of course I feel anxious with the NSA following me around the clock"). Other conditions (medical, drug induced, other primary psychiatric disorders, including other psychotic or mood disorders) cannot better explain the clinical picture.[30]

28 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

29 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

30 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

Subtypes/Specifiers

- Erotomanic type: the patient erroneously believes that another person is in love with him/her
- Grandiose type: the patient erroneously believes that he/she possesses enormous wealth, power, authority, knowledge, or has a special relationship to a deity or famous person
- Jealous type: the patient erroneously believes that his/her partner is unfaithful
- Persecutory type: the patient erroneously that he/she is targeted for punishment or retaliation
- Somatic type: the patient erroneously believes that he/she has a medical condition or body deformity that is overlooked or misdiagnosed
- Mixed type: delusions characteristic of more than one of the above types but without any one dominating theme
- Unspecified type[31]

Epidemiology

Rare. According to DSM-IV-TR estimated around 0.03% in the general population; 1-2% of all inpatient psychiatric admissions. The most common subtype is the persecutory type.[32]

Treatment Considerations

Hospitalization is recommended if the acute psychotic symptoms result in danger to self or others or significant impairment.

Prognosis

Variable: the jealous type may wane and wax or remit; the persecutory type is often chronic.[33]

2.9 Shared Psychotic Disorder (Folie à Deux)

Clinical Manifestations and Diagnostic Considerations

Mental status examination is significant for non-bizarre delusions but otherwise is within normal limits. There are minimal associated mood or anxiety symptoms; if present such symptoms appear secondary to the tenaciously held delusional beliefs. History is significant for a close relationship with another person who presents with similar delusional beliefs

31 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

32 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

33 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

and meets criteria for a psychotic disorder. The patient who first presents with delusional symptoms is designated as the "primary," the "secondary" follows. Also, usually, the primary is dominant in his/her relationship with the secondary, who acts as a more passive recipient. For example, a parent with schizophrenia and chronic paranoid delusions about FBI surveillance may be the primary while his/her child, who only recently started to believe that indeed there are FBI cameras hidden on their property, is the secondary. Other diagnoses, including medical or drug induced disorders as well as other psychotic or mood disorders, should be excluded if folie à deux is to be diagnosed.[34]

Epidemiology

Rare overall but statistics may be misleading due to under-reporting. Preliminary data suggest an increased prevalence in women.[35]

Treatment Considerations

Hospitalization is recommended if the acute psychotic symptoms result in danger to self or others or significant impairment. Usually removing the secondary from the primary's environment is sufficient to promote complete remission of symptoms. In addition, the primary's condition should be treated as indicated. Interestingly, a remission of the primary's symptoms is followed by the remission of the secondary's delusional beliefs.

Prognosis

When the secondary is separated from the primary the prognosis is good.[36]

2.10 References

34 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

35 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

36 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR. PsychiatryOnline.com Online ISBN 0-89042-334-2. Accessed 03/01/2011

3 Mood Disorders

3.0.1 Introduction

Manic-depressive illness is known since the era of Hippocrates (460–357 BC), Galen (131–201 AD) and Areteus from Kappadokia, and is described in ancient medical texts. Some authors believe that King Saul was also suffering from this disease and David used to relieve his depression by playing music for him. The ancient Greeks and Romans coined the terms "melancholia" and "mania." Hippocrates was the first to describe melancholia which is the Greek word for "black bile" and simultaneously postulated a biochemical origin according to the scientific frame of that era, linking it to Saturn and the autumn.

Mania was described as madness with elevated mood but it included a broad spectrum of excited psychotic states the way we understand them today. Soranus was the first to describe mixed states. Aretaeus of Cappadocia (2nd century AD) is considered to be the one who strongly connected melancholia with mania and made a description of manic episodes very close to the modern approach, including psychotic features and seasonality.

Another interesting element in the theories that emerged during antiquity was the concept of temperament which was originally based on harmony and balance of the four humors, of which the sanguine humor was considered to be the healthiest but also predisposing to mania. The melancholic temperament was linked to black bile and was considered to predispose to melancholia. Since the time of Aristotle (384–322 BC), the melancholic temperament was linked to creativity.

During the 10th and 11th century AD the Arab scholars dominated (Ishaq Ibn Imran, Avicenna and others). In 1621 Robert Burton wrote the first English-speaking text on the field of mood disorders "The Anatomy of Melancholy." Later, the works of Jean-Philippe Esquirol (1772-1840), Benjamin Rush (1745–1813), Henry Maudsley (1835–1918), Jean-Pierre Falret (1794-1870) and Jules Gabriel Francois Baillarger (1809-1890) established the connection between depression and mania. Finally, Emil Kraepelin (1856–1926) established manic-depressive illness as a nosological entity (and separated it from schizophrenia) on the basis of heredity, longitudinal follow-up and a supposed favorable outcome.

Recent research data has reshaped our definition and understanding of bipolar and other mood disorders. Today the suboptimal outcome of mood disorders is well documented, especially in relationship to younger age of onset and to alcohol and substance abuse. Suicide is another major concern since up to 75% of patients who commit suicide suffer from some type of mood disorder.

Recently the World Health Organization (WHO) has ranked neuropsychiatric disorders as one of the most disability inducing causes world-wide, more disabling than cancer and cardiovascular diseases, and equal to injuries from all causes (World Health Organization,

2003). Affective disorders combined are the most disabling neuropsychiatric conditions and one of the 4 leading disability causes.

3.0.2 Phenomenology

Epidemiology

DSM-IV-TR unipolar major depressive disorder (U-MDD) is reported to be the most common mood disorder (Weissman et al. 1996). The overall current prevalence of MDD is estimated to be 4.7% for males and 6% for females and the annual incidence is around 1.59%. Depression of any type may afflict 10-25% of females and 5-12% of males at some time during their lives with the rates varying widely and depending on ethnic background, type of residential area, gender, age, social support and general somatic health status. The results of the US Epidemiologic Catchment Area (ECA) study suggest that disabling mood disorders affect as high as 5-8% of the general population and that if milder depression is included then the lifetime prevalence increases to 17% (National Comorbidity Study -NCS). When subclinical mood states are included, it is reported that one third of the general population will be affected (Dryman & Eaton, 1991; Eaton, Dryman, Sorenson, & McCutcheon, 1989; Eaton, Kramer et al. 1989). In spite of treatment, disability rates are high and suicide occurs in about 15% of patients, especially in men. Conversely, a significant proportion of suicide victims suffer from some kind of depressive state (Parkar, Dawani, & Weiss, 2006; Seguin et al. 2006; Zonda, 2006). For some people depression is a single episode in life but around half of those experiencing an episode will experience more in the future, and the likelihood after the second episode is to experience a third episode within a decade or so. One third of patients will recover within the first 2-3 months, another third will need 6-8 months and around 15% of patients will not have recovered after 2 years, and they are likely to develop a chronic course (Kruijshaar et al. 2005; Patten & Lee, 2004, 2005; Patten, 2006; Patten et al. 2006; Patten, 2007; Waraich, Goldner, Somers, & Hsu, 2004; Wulsin, Vaillant, & Wells, 1999).

The epidemiological data concerning the risk factors for MDD is rich but inconclusive. Women are twice as likely as men to experience an episode of MDD (Coryell, Endicott, Andreasen, & Keller, 1985; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Tennant, 1985; Weissman et al. 1988) and age plays a complex role (Koeniq, Meador, Cotlen, & Blazer, 1988). MDD has an average age of onset between 20 and 40 years while bipolar disorder may appear more frequently in the early 20's (Weissman et al. 1988). The effect of socioeconomic status is weak if it exists at all (Hollingshead & Redlich, 2007). Marital status appears to be one of the most consistent risk factors for MDD with recently widowed, separated and divorced persons being at higher risk, and single and married persons at lower risk. A family history of MDD, especially in first-degree relatives, constitutes a major risk factor along with family history of suicide and alcoholism. Early childhood abuse per se may be related to increased neuroendocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood (Heim et al. 2002). Some personality features (introversion, worry, dependency and interpersonal sensitivity) as well as social stressors and social support also constitute risk factors (Farmer et al. 2001; Iacovides, Fountoulakis, Fotiou, & Kaprinis, 2002; Paykel, 1994, 2001a, 2001b). Life events (especially loss and bereavement), chronic stress (financial, family and interpersonal difficulties), and

daily hassles as well as routine changes even due to positive events (e.g., change in residency due to promotion at work) all constitute risk factors (Fotiou, Fountoulakis, Iacovides, & Kaprinis, 2003; Rijsdijk et al.2001). In addition, it has been reported that adolescent life events predicted an increased risk for major depression diagnosis in early adulthood (Pine, Cohen, Johnson, & Brook, 2002) The conclusion from few available community-based studies suggested that younger age, low social class, negative and stressful life events linked to the family were associated with increased risk of new onset depression (Friis, Wittchen, Pfister, & Lieb, 2002).

Originally it has been suggested that the classic manic depressive psychosis had a prevalence of around 1% (0.4-1.6%). However, today we know that the true prevalence depends on the definition, and to an extent, the sub-threshold bipolar cases and pseudo-unipolar patients. In addition, personality disorders (PDs), especially borderline personality disorder, are included under the umbrella of the bipolar spectrum or under unipolar depression. Another open question is whether the avoidant and the dependent PDs constitute real PDs or instead are residuals of a previously experienced major depressive episode. This is because these two PDs have been detected only in patient populations and not really in general population samples.

DSM-IV-TR Bipolar disorder (BD) type I and type II have a combined prevalence rate of up to 3.7%. The literature on the lifetime prevalence of BD suggests an overall rate of 3-6.5% including a wider spectrum of bipolarity in comparison to the DSM-IV-TR definition (Acorn, 1993; Angst, 1998; Judd & Akiskal, 2003).

As for other risk factors (Laursen, Munk-Olsen, Nordentoft, & Bo Mortensen, 2007), although younger age, marital status (separated/divorced) and negative life events have been suggested to play a role, perhaps the best proven risk factor is the genetic transmission of bipolar disorder, which is much higher than that of MDD.

Clinical symptoms and classification

The onset of mood episodes can be acute or insidious, and emerge from a low-grade, intermittent, and protracted mood substrate which can resemble a dysthymic or cyclothymic state or even personality features (Fogel, Eaton, & Ford, 2006). These mood states can also prevail during the inter-episode period and may give rise to low quality of life, interpersonal conflicts and significant global disability. Furthermore, these subthreshold disorders are quite frequent in the families of patients (Shankman, Klein, Lewinsohn, Seeley, & Small, 2008). Dysthymic and cyclothymic disorders are recognized by contemporary classification systems as separate diagnostic entities and often do not lead to the manifestation of a full blown mood episode. Dysthymic disorder corresponds largely to a chronic mild form of depression with a relatively stable social functioning.

Bipolar disorders (previously called manic-depressive psychosis) consists of at least one hypomanic, manic, or mixed episode. Mixed episodes represent a simultaneous mixture of depressive and manic or hypomanic manifestations. Although a minority of patients experience only manic episodes, most bipolar disorder (BD) patients experience episodes of both polarity.

The classical definition of BD suggests that this disorder is characterized by the presence and alteration of manic and depressive episodes with a return to premorbid level of functioning between the episodes and a favorable outcome in comparison to schizophrenia (Kraepelin, 1921). Today we know that this is not always the case (Tohen, Waternaux, & Tsuang, 1990). The Kraepelinian concept largely corresponds to BD type I (BD-I) according to DSM-IV-TR (American Psychiatric Association, 2000). Typically, BD-I starts before the age of 40. Frequently the correct diagnosis is made after several years because the first episode is psychotic-like or depressive and the diagnosis is only evident after a manic or mixed episode emerges. Another type, BD-II is officially recognized as a bipolar illness subtype and it is characterized by the presence of hypomanic instead of manic episodes. However, it is important to note that according to DSM-IV-TR (American Psychiatric Association, 2000) hypomania is defined mainly in terms of a shorter duration of the episode. BD-II is more prevalent than BD-I disorder. An additional complicating factor for diagnosis is that patients usually experience hypomania as a recovery from depression and almost always as a pleasant ego-syntonic mood state.

Depressive episodes are considered to be the second diagnostic pillar of BD. However, in contrast to manic episodes which lead to the diagnosis of BD immediately, depressive episodes pose a dilemma to the clinician regarding whether or not he or she faces a unipolar depression or a BD. This is an important dilemma to solve since the treatment of these disorders differ. However, it has been estimated that more than half of patients originally manifesting a depressive episode will turn out to have BD in the next 20 years (Angst, Sellaro, Stassen, & Gamma, 2005). Unipolar-depressed patients who later "convert" to BD over time, as well as patients with bipolar depression manifest more frequently "atypical" features of depression (hypersomnia, hyperphagia, leaden paralysis, long term interpersonal rejection sensitivity, psychomotor retardation, psychotic features, pathological guilt and mood lability)(Perugi et al. 1998). BD patients also tend to have earlier age of onset, more prior episodes of depression, shorter depressive episodes, and family history of BD (Akiskal & Benazzi, 2008; Mitchell, Goodwin, Johnson, & Hirschfeld, 2008). Family history of BD is a strong predictor of bipolarity even in children and adolescents (Geller, Fox, & Clark, 1994). DSM-IV-TR recognizes atypical features of depression (Davidson, Miller, Turnbull, & Sullivan, 1982; Fountoulakis, Iacovides, Nimatoudis, Kaprinis, & Ierodiakonou, 1999; Thase, 2007). This depressive subtype includes the presence of personality-like features such as long-term interpersonal rejection sensitivity, and somatic symptoms such as reverse vegetative signs, hypersomnia, increased appetite, weight gain and leaden paralysis. There is strong evidence linking atypical depression to BD-II (Akiskal & Benazzi, 2005).

Mixed episodes are also considered to be part of the BD picture, and according to DSM-IV-TR are defined as the co-existence of both depressive and manic symptoms to the extent that the criteria for both a manic and a depressed episode are fulfilled (Akiskal & Benazzi, 2004). Alterations in mood characterize several other DSM disorders which have a bipolar character. These include cyclothymic disorder and borderline personality disorder. However, there is a constellation of types of affective episodes which are not part of the official classification and they are so prevalent in real life clinical practice that many authors consider them to be the rule rather than the exception.

Sometimes there is a mixture of manic and depressive symptoms in a combination which does not fulfill the specific DSM criteria for a manic, depressive or mixed episode. Therefore, the

only possible diagnosis is that of a Not-Otherwise-Specified (NOS) mood episode (Akiskal, 1996; Akiskal et al. 1998).

Often manic symptoms can go unnoticed by the clinician because instead of being hyperthymic, the mood is irritable and is diluted in the presence of depressed thought content and suicidal ideation. Such a presentation may lead the clinician to the diagnosis of anxious or agitated depression, or worse, of a personality disorder, instead of a mixed or mixed-NOS mood episode. Frequently, this irritable mood can result in aggressive behavior especially if confronted or rejected while having grandiose or paranoid delusions. These patients may be the most aggressive seen in the emergency room (Maj, Pirozzi, Magliano, & Bartoli, 2003; Sato, Bottlender, Kleindienst, & Moller, 2005).

There is evidence that an excited/irritable state can develop when antidepressants, especially dual action ones, are used. Many patients will not develop a classic manic episode in response; many will either develop a full blown mixed episode or more likely a DSM sub-threshold mixed-NOS episode with the presence of a small number of manic symptoms in combination with depression, especially agitation, and this state may persist and worsen if more aggressive antidepressant treatment is tried.

Rapid cycling refers to patients suffering from at least 4 mood episodes in a year. It seems that females are more often rapid-cyclers as well as higher social class subjects. In essence, these patients tend to be symptomatic most of their life and are considered to be refractory to lithium. The diagnosis may elude for prolonged periods of time and the patients can receive the diagnosis of a personality disorder or cyclothymia. Treatment of rapid cycling is based on a complex, delicate and difficult to design multiple pharmacotherapy which includes atypical antipsychotics, anticonvulsants and even antidepressants, although the latter are believed to induce rapid cycling (Bauer et al. 1994).

Psychotic features are common in bipolar patients and may include delusions or hallucinations of any type. They can either be mood congruent or mood incongruent. In order to make the diagnosis of schizoaffective disorder according to DSM-IV-TR there must be a psychotic episode in the absence of prominent mood symptoms. However, according to ICD-10 this diagnostic boundary is vague and differential classification is often difficult.

Alcohol and substance abuse are very common problems in BD. Drug abuse may precipitate an earlier onset of BD-I in those who already have a familial predisposition for mania. Alcohol abuse may be present in more than half of patients. It seems that frequently this represents self-medication efforts and abuse is particularly problematic during adolescence and early adulthood. At this age period substance and alcohol abuse may not only suppress symptoms but also enhance specific desired activities (e.g., high school performance, sex etc.). Alcohol abuse can cause further disinhibition and may cause the patient to manifest physical aggression especially towards the family, with "crimes of passion" being the most tragic result. BD patients tend to abuse stimulant drugs. Familial diathesis for mania is significantly associated with the abuse of alcohol and drugs and it is possible that there is a common familial-genetic diathesis for a subtype of BD-I, alcohol and stimulant abuse (Winokur et al.1998).

The cognitive deficits of BD patients have not been studied adequately. However, in contrast to the early Kraepelinian concept for a favorable functioning outcome, recent studies suggest there is a significant degree of psychosocial impairment even when patients are euthymic and report that only a minority achieves complete functional recovery (Daban et al. 2006;

Goldberg, Harrow, & Grossman, 1995a, 1995b; Keck et al. 1998; Martinez-Aran et al. 2007; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2007; Strakowski et al. 1998). Cognitive impairment is reported to exist in both BD-I and BD-II patients, although more so in the BD-I group and this is true even during the euthymic period. The cognitive deficit can be worse during the manic phase but it is present during all phases of the illness (Dixon, Kravariti, Frith, Murray, & McGuire, 2004; Malhi, Ivanovski, Szekeres, & Olley, 2004). However, when compared to patients with schizophrenia, BD patients demonstrate a lesser degree of deficits, particularly concerning premorbid and current intelligence quotient and perhaps attention, verbal memory,verbal fluency and executive functions (Mur et al. 2007; Torrent et al. 2006). The pattern of the neurocognitive deficit implicates the prefrontal cortex and temporo-limbic structures, especially ventromedial areas as well as the amygdala and the hippocampus.

Mood disorders are characterized by a constellation of symptoms and signs. The terms "depressed mood," "anhedonia" and "elevated mood" are central to the definition and diagnosis of these disorders.

Mood

- **Euthymia** refers to the normal range of mood, and the absence of any disorder.
- **Mourning** refers to the experience of sadness as a consequence of a loss of a loved one. It includes, crying, sadness, preoccupation with the lost person and related memories.
- **Depressed mood** means that the patient experiences a "negative" and unpleasant affect, and in English and other western cultures and languages the words (or their linguistic equivalents) "depressed," "anguished," "mournful," "sad," "anxious," "blues" are used. The word "depressed" is increasingly used because of the higher information (partially because of the internet) the public has today on depression. The way patient uses describes this experience depends on his/her cultural and educational background, and can focus on bodily function or on existential and interpersonal dysphoria and difficulties. Somatic complaints are more prominent in milder cases usually seen in the primary care setting, particularly in patients with anxious depression. These patients were considered to suffer from "masked" depression.
- **Anhedonia** refers to the inability to experience normal emotions. Frequently, patients with anhedonia are incapable of even feeling the depressed affect and they can't even cry. The patient abandons activities which in the past were a source of joy and gives up interest in life. Patients with more severe depression are indifferent even concerning their children or spouse and isolate themselves. The difference from the flat (blunted) affect seen in schizophrenia is that anhedonia is itself painful. As depression starts remitting, anhedonia is one of the first symptoms to remit.
- **Elevated mood** refers to a state of elation, overconfidence, and enjoyment, with the person being cheerful, laughing and making happy and expressive gestures. It is not always pathological.
- **Euphoria** refers to a pathologically too much elevated mood that is inappropriate to real events. It is considered to constitute the opposite pole of "depressed mood" with "normality" in the middle. Experiencing a euphoric mood is pleasant thus patients are reluctant to receive treatment.

- **Expansive mood** is a condition with the patient expressing his/her feelings without restraint and control and behavior is usually colored by grandiose thoughts.
- **Emotional lability** refers to unstable and rapidly changing emotions because of hyper-reactivity to environmental stimuli. It is not always pathological
- **Irritable mood** is a state in which the person is easily annoyed by external stimuli and expresses anger and hostility at a low threshold. The presence of an irritable mood is often the cause for misdiagnosis of the patient, especially in combination with lability and mixed states.

Psychomotor Disorder

- **Flight of ideas** refers to an acceleration of the thinking processes, and it manifests itself in the form of rapid speech. Speech can be coherent and thoughts unusually sharp. However, when speed is excessively high, they both become incoherent and fragmented with content changing abruptly. Associations can be based on rhyme or chance perceptions.
- **Psychomotor acceleration** is considered to be the hallmark of mania, characterized by excessive activity (which is goal directed, high energy and endurance) as well as rapid, pressured speech.
- In comparison, **psychomotor agitation** also refers to a both mental and physical over-activity (pressured speech, restlessness, increased motor behavior) usually accompanied by a feeling of an inner turmoil or severe anxiety, with the intensity being so great that in spite of the fact that the patient has normal arousal, most if not all of this activity is purposeless.
- **Psychomotor slowing** means that the patient is inert and slow, both physically and mentally, but this does not always have an effect on overall performance although everything is done with much effort
- When psychomotor slowing is excessive, then **psychomotor retardation** appears and it includes reduction or disappearance of spontaneous motor activity, slumped posture and gaze, reduced and slow speech, and great fatigue.
- **Stupor** appears in younger patients when the psychomotor retardation is so extreme that they are unable to perform even basic everyday tasks. In more severe cases, motoric immobility occurs.
- **Catatonia** is defined as a complex condition which can include diverse symptoms and signs such as motoric immobility or on the contrary excessive purposeless motor activity not influenced by external stimuli, motiveless negativism, mutism, peculiar or stereotyped movements, mannerisms, grimacing and sometimes echolalia or echopraxia.
- **Fatigue** is a common problem in all mental disorders but especially in mood disorders and includes feeling tired or weak, sleepy, and sometimes irritable.

Neurocognitive Disorder

The term "neurocognitive" is often used with reference to higher cognitive function, such as attention, concentration, memory, praxis etc., and in psychiatry in contrast to the term "cognitive" which often is used with reference to the thought content or style and relates to

cognitive therapy. Bipolar patients constitute a clinically heterogeneous group. However, they seem to perform poorly on most neuropsychological tests in comparison to healthy controls. They seem to suffer from deficits especially related to attention, inhibitory control, spatial working memory, semantic verbal fluency, verbal learning and memory, and maybe executive function (especially when considering the more severe and psychotic end of the bipolar spectrum). Verbal memory and probably executive function impairments may represent a trait rather than a state marker (Martinez-Aran et al. 2007; Martinez-Aran et al. 2008).

In extreme cases, neurocognitive disorder is so severe, especially in elderly patients that the picture resembles that of a dementing disease, thus is called "pseudodementia." However, it seems that at least half of these patients do in fact suffer from a dementing process at its early stages and later they manifest a formal dementia syndrome (Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993; Alexopoulos, Young, & Meyers, 1993; Bajulaiye & Alexopoulos, 1994; Reifler, 2000; Saez-Fonseca, Lee, & Walker, 2007) If one looks at the problem from another point of view, depression with mild cognitive disorder may be either the first manifestation or a risk factor for the development of dementia, especially when combined with a family history of dementia (Tsolaki, Fountoulakis, Chantzi, & Kazis, 1997; VanOjen & Hooijer, 1995; VanOjen, Hooijer, & . , 1995).

Thought Disorder

- **Depressive thought content:** depressed patients are characterized by a negative evaluation of the self, the world, and the future (the negative cognitive triad). In this frame, the depressive thought content includes pessimism, low self-esteem and low self-confidence, ideas of loss, deprivation and guilt, helplessness and hopelessness, and ultimately thoughts of death and suicide. The extent to which this negative way of thinking is primary or secondary is a matter for debate.
- **Clang association:** refers to the condition when the patient's thoughts association and subsequently the speech are directed by the sound of a word rather than by its meaning. Therefore, words are not connected in a logical way and punning and rhyming serve as the drive.
- **Thoughts of guilt** concern self-reproach, self accussation and feeling the need for punishment. Thoughts and feelings of guilt are to largely normal and they can appear during a mood disorder because of the disability the disorder causes and the inability of the patient to fulfill his/her obligations towards significant others. In this frame patients may also feel shame. However, when the intensity and the content is excessive or even inappropriate then thoughts of guilt should be considered to be part of the symptoms and in more severe cases these thoughts may take on a delusional character.
- **Thoughts of death** are particularly important because they may eventually lead to suicidal behavior. The common belief that inquiring about such thoughts provokes suicidal behavior has no scientific basis. On the contrary, patients are often relieved this way. These thoughts include thoughts that the person will die and often the wish to die in some way so as to leave the suffering behind; this way they lead to suicidal ideation.
- **Suicidal ideation** refers to specific thoughts of killing oneself. It has many different forms, ranging from indirect expression (e.g., a wish not to wake up, or to die from a disease or an accident), to suicidal obsessions (urges or impulses to destroy oneself) and

finally to elaborate planning of suicide. Some patients behave in a passive self-destructing way (e.g., careless driving or walking) while others plan their death in detail leaving notes and making sure no help will come on time.

- **Manic thinking** is excessively positive and optimistic. It is characterized by inflated self-esteem, grandiose sense (concerning importance, power, knowledge, or identity), over-confidence and sense of high achievements and abilities. Manic patients are refractory to explanations, confrontation, and to a significant extent they lack self-examination and insight; because of this lack of insight, mania nearly always, sooner or later acquires a delusional character.

Psychotic Symptoms

Psychotic features include delusions and hallucinations and both can be mood congruent or non-congruent depending on their content. Mood congruent psychotic features include those entirely consistent with the thought content (either manic or depressive) while mood incongruent are largely unrelated to it. Psychotic features are not uncommon in mood disorders, especially in bipolar disorder and delusions are relatively more common than hallucinations.

- **Mood-congruent depressive delusions:** often depressed thoughts can acquire a delusional severity and delusions congruent with depressive mood appear. Their content concerns inappropriate or over-exaggerated thoughts of guilt, sin, worthlessness, poverty and somatic health. Delusions concerning persecution and jealousy, although seemingly non-congruent, can also be mood congruent if they can be explained by, or strongly related to, thoughts of sin, guilt, jealousy or worthlessness. This kind of delusional thought makes a parent kill his/her family so as to save them from moral or physical corruption and then he/she commits suicide.
- **Nihilistic delusions** (Cotard delusion or Cotard's syndrome, negation delusion are related to depressive mood and concern the delusional belief that all or parts of the patient's body are missing or rotten or decomposing, their internal organs are rotten or solidifying or are actually dead; the world and everything related to it have ceased to exist.
- **Mood-congruent manic delusions:** during manic episodes usually the thought content becomes delusional and includes delusions of exceptional mental and physical fitness or special talents. It may also include delusions of wealth, some kind of grandiose identity or importance. Sometimes the delusion can be so excessive that the identity itself changes (e.g., the patient believes that he is the incarnation of a messiah or a prophet etc.) Delusions of reference and persecution are considered to be mood-congruent on the basis of the belief that jealousy of the others at their special abilities is the cause of problems.
- **Mood-incongruent delusions:** various delusional ideas seemingly non-congruent (e.g., ideas of persecution or reference) can eventually be understood as arising from the grandiose sense of self and the belief of the patient that this importance causes the others to envy. However, sometimes there are delusions with no association to current mood (e.g., bizarre delusions without contextual relationship to mood). Sometimes a mixed mood episode can manifest itself with mood-incongruent delusions e.g., grandiose delusions in the presence of depressed mood.

- **Depressive mood-congruent hallucinations** are hallucinations consistent with either a depressed (e.g., voices accusing or humiliating) or manic mood (e.g., voices praising). Depressive mood-congruent hallucinations have an unpleasant content and they cause significant additional distress to the patient. Sometimes they command the patient to commit suicide and even dictate the method.
- **Manic mood-congruent hallucinations:** sometimes a manic mood causes such a vivid internal experience that the patient feels he/she can hear or see his/her own thoughts (e.g., hear hymns or live in the paradise).
- **Mood-incongruent hallucinations** refer to hallucinations unrelated to the current mood state.
- **Insight:** classically, depressive episodes are characterized by a fair degree of insight with the exception of the more severe psychotic cases. On the contrary, manic episodes are routinely characterized by a significant lack of insight and thus clinicians must routinely obtain basic information from significant others. This lack of insight may lead to refusal of treatment and to the need for involuntary admission to hospital.

Somatic and Neurovegetative Symptoms

Depressed patients often manifest changes in appetite, sleep and sexual functioning. Circadian rhythms are also disrupted. The classical notion of depression which is closer to melancholia includes reduction in all these functions; however, recently the "atypical" form of depression was described and this form includes an increase in these neurovegetative functions; that is overeating and oversleeping along with interpersonal rejection sensitivity which is a "personality-like" feature.

- **Anorexia and weight loss:** are considered to be reliable signs of depression. They can both be considered in the frame of a generalized inability to enjoy things (anhedonia). Weight loss is seen sometimes in paranoid patients who are afraid that food is poisoned and this should not be confused with anorexia and weight loss in the frame of depression. Weight loss is also frequent in cases of malignant disease so a full medical investigation should accompany any patient with changes in appetite or weight.
- **Weight gain** has been, relatively recently, recognized as a depressive feature and could be the result of overeating, decreased activity, or both. Apart from its devastating effect on the self-confidence and self-image, it can worsen the general somatic health especially in patients that become obese and suffer from metabolic syndrome.
- **Insomnia** is one of the hallmarks of depression and one of its most disturbing features. There are many types of insomnia that is, difficulty falling asleep (initial insomnia), multiple awakenings during the night (middle insomnia) or early morning awakening (terminal insomnia). Insomnia prolongs the depressive agony round the clock. Some patients try to self-medicate and solve the problem by alcohol or drug abuse (sedatives or hypnotics) but both eventually worsen the problem, partially because of tolerance and dependence problems and partially because they both further destroy the architecture of sleep. Unipolar depressed patients tend to exhibit insomnia stereotypically episode after episode and characteristically, in spite of extreme fatigue, they rarely oversleep.
- **Hyposomnia:** the term suggests a decreased need for sleep. That is, the patient feels energetic on awakening even though he slept for short periods. Some patients feel fresh

and energetic even though he/she haven't slept for days. This condition is usually seen during manic episodes and sometimes it heralds the beginning of such an episode.

- **Hypersomnia:** some patients, especially younger ones and females, often sleep too much and find it difficult to get up from the bed in the morning. Along with the other atypical features it is considered to be a marker for an underlying bipolar illness even in cases where no other bipolar feature is present. This condition should be differentially diagnosed from a number of medical conditions including narcolepsy and the Klein-Levin syndrome. In spite of prolonged sleep, depressed patients are characteristically tired in the morning, meaning that even prolonged sleep is not refreshing for them. The change in the pattern of sleep disruption with insomnia alternating with hypersomnia or hyposomnia suggests the presence of a bipolar illness rather than a unipolar depression.
- **Circadian dysregulation:** although many circadian functions can be disrupted in depressed patients, mainly the disturbance of sleep rhythms has been adequately studied. This disturbance includes deficits in delta sleep and more intense rapid eye movement (REM) activity during the first third of the night. A marked shortening of REM latency (that is the time from the onset of sleep to the first REM period) is considered to be characteristic for depression of any type, and seen even in remitted depressive patients and their healthy relatives.
- **Seasonality:** seasonal (especially autumn-winter) emergence or worsening of depression has been recognized since antiquity and mood has been related to the period of the year. Most patients seem to experience increased energy and activation during spring and the opposite during the fall and winter. Usually patients with strong seasonality also have reverse neurovegetative symptoms (fatigue, crave sugars, overeat and oversleep). In some patients seasonality is so concrete and important that modern classification includes a seasonal pattern for mood disorders.
- **Sexual dysfunction:** depressed patients classically report a decreased sexual desire and activity while additionally some women manifest a temporary interruption of their menses. Sexual dysfunction especially in females can lead to marital conflict and a psychodynamic/psychotherapeutically oriented therapist can mistakenly ascribe depression to the marital conflict with profound negative effects on the therapeutic outcome. Treating the sexual dysfunction or its consequences and leaving depression untreated is not uncommon and includes even surgical or unusual therapeutic interventions. An additional problem is that treatment with antidepressants often has sexual dysfunction as an adverse effect. The recent emergence of agents that treat impotence (e.g., sildenafil, tadalafil) could add a new method to treat this problematic symptom but this should never move the focus of treatment away from depression.
- **Increased sexual desire and activity** is typical for manic episodes, but also a subgroup of depressed patients may manifest increased sexual drive or activity and usually they also manifest other atypical or "reversed" features. Therefore, if seen in the frame of depression it heralds the presence of a depressive mixed episode. The increased sexual appetite usually leads to sexual indiscretion accompanied by a risky sexual life, often leading to marital problems, multiple separations or divorces, alcohol and drug abuse, gambling and sexually transmitted diseases like AIDS.

Behavioral Disorder

- **Logorrhea** refers to pressured, excessive and not always coherent speech, which is often uncontrollable. It is observed during manic episodes. Speech can be completely incomprehensible, with destroyed syntax and loose associations, often posing diagnostic dilemmas (e.g., from stroke). Other similar terms used are tachylogia, verbomania, volubility.
- **Impulsive behavior:** during mood episodes, either manic, depressive or mixed, patients tend to exhibit impulsive behavior. Especially during manic episodes they tend to be impulsive, disinhibited, and meddlesome. They are intrusive with increased involvement with others, poor social judgment and engage in a variety of activities without control or restraint (including aggression, sex, gambling, drug and alcohol abuse, spending, making gifts, risk taking, travelling etc.) Impulsive behavior is symptom that causes most problems and especially financial and interpersonal. In some cases even suicide may be acted on an impulsive basis.

The terms "endogenous depression," "neurotic depression," "anxious depression," "involutional melancholia," "psychotic depressive reaction" are not included in modern classification systems for a variety of reasons. The term "neurasthenia" is maintained in ICD-10 but its meaning is vague.

It seems that the psychotic melancholic subtype is the most stable type of depression repeating itself across episodes (Coryell et al. 1994). Almost a third of all major depressive episodes do not recur and it seems that recurrent depression is more familial with on average 6 months episode duration and a varying inter-episode interval length. A significant proportion of patients remain symptomatic and disabled, many of them suffering from subsyndromal depression (Judd et al. 1998). Around 15% develops psychotic features

Comorbidity

Large epidemiological studies and clinical experience suggest that mood disorders either co-exist or overlap considerably with anxiety disorders. Anxiety disorders can occur during a depressive episode, may be a precursor to it, or may appear during the future course of a mood disorder. Several authors suggest there is a common diathesis connecting mood and anxiety disorders with more recent data suggesting a strong link between BD-II and panic, obsessive-compulsive disorder, and social phobia.

All mood disorders but especially bipolar disorder are highly likely be comorbid with alcohol and drug (mainly stimulants) abuse, usually in the frame of a self-treatment effort from the side of the patient (Winokur et al. 1998).

Somatic illness frequently co-exists with depression and anxiety and the mood disorder has a profound negative impact on the outcome of the somatic illness. The therapist should also suspect clinical depression in all patients who refuse to participate in medical care.

Classification

The International Classification of Diseases, 10th version (ICD-10) includes sets of criteria for mood disorders, which are used throughout the world and constitute the official method of reporting health statistics. They are overlapping with the Diagnostic and Statistical

Manual of Mental Disorders 4th edition, Text Revision (DSM-IV-TR) criteria; however, important differences do exist.

The basis of the classification in both systems is the definition of the depressive and manic/hypomanic episodes. The two systems describe mood disorders as follows:

In the ICD-10 the depressive episode is defined as follows:

A. DEPRESSIVE EPISODE

General criteria for a depressive episode:

G1. The depressive episode should last for at least 2 weeks.

G2. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode (F30._) at any time in the individual's life.

G3. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00-F09).

F32: **Depressive episode**

A. The general criteria for depressive episode (F32) must be met.

B. At least two of the following three symptoms must be present:

(1) depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks;

(2) loss of interest or pleasure in activities that are normally pleasurable;

(3) decreased energy or increased fatigability.

C. An additional symptom or symptoms from the following list should be present, to give a total of at least: four for **mild** (F32.0), six for **moderate** (F32.1) and eight for **severe** (F32.2 or F32.3 - depending on psychotic symptoms)depressive episode:

(1) loss of confidence or self-esteem;

(2) unreasonable feelings of self-reproach or excessive and inappropriate guilt;

(3) recurrent thoughts of death or suicide, or any suicidal behavior;

(4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation;

(5) change in psychomotor activity, with agitation or retardation (either subjective or objective);

(6) sleep disturbance of any type;

(7) change in appetite (decrease or increase) with corresponding weight change.

A fifth character may be used to specify the presence or absence of the "somatic syndrome":

F32.x0 Without somatic syndrome

F32.x1 With somatic syndrome

F32.2: Without psychotic symptoms (only for severe depressive episode)

F32.3: With psychotic symptoms (only for severe depressive episode)

F32.3: **Severe depressive episode with psychotic symptoms**

A. The general criteria for depressive episode (F32) must be met.

B. The criteria for severe depressive episode without psychotic symptoms (F32.2) must be met with the exception of criterion D.

C. The criteria for schizophrenia (F20.0-F20.3) or schizoaffective disorder, depressive type (F25.1), are not met.

D. Either of the following must be present:

(1) delusions or hallucinations, other than those listed as typically schizophrenic in criterion G1(1)b, c, and d for general criteria for F20.0-F20.3 (i.e., delusions other than those that are completely impossible or culturally inappropriate and hallucinations that are not in the third person or giving a running commentary); the commonest examples are those with depressive, guilty, hypochondriacal, nihilistic, self-referential, or persecutory content;

(2) depressive stupor.

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with mood:

F32.30: **With mood-congruent psychotic symptoms** (i.e., delusions of guilt, worthlessness, bodily disease, or impending disaster, derisive or condemnatory auditory hallucinations)

F32.31: **With mood-incongruent psychotic symptoms** (i.e., persecutory or self-referential delusions and hallucinations without an affective content)

F32.8: **Other depressive episodes:** Episodes should be included here which do not fit the descriptions given for depressive episodes, but for which the overall diagnostic impression indicates that they are depressive in nature. Examples included fluctuating mixtures of depressive symptoms (particularly those of the somatic syndrome) with nondiagnostic symptoms such as tension, worry, and distress, and mixtures of somatic depressive symptoms with persistent pain or fatigue not due to organic causes (as sometimes seen in general hospital services).

F32.9: **Depressive episode, unspecified**

Somatic syndrome

Some depressive symptoms are widely regarded as having special clinical significance and are here called "somatic" (terms such as biological, vital, melancholic, or endogenomorphic are used for this syndrome in other classifications). A fifth character may be used to specify the presence or absence of the somatic syndrome. To qualify for the somatic syndrome, four of the following symptoms should be present:

(1) marked loss of interest or pleasure in activities that are normally pleasurable;

(2) lack of emotional reactions to events or activities that normally produce an emotional response;

(3) waking in the morning 2 hours or more before the usual time;

(4) depression worse in the morning;

(5) objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people); (6) marked loss of appetite;

(7) weight loss (5% or more of body weight in the past month);

(8) marked loss of libido.

In The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines, the presence or absence of the somatic syndrome is not specified for severe depressive episode, since it is presumed to be present in most cases. For research purposes, however, it may be advisable to allow for the coding of the absence of the somatic syndrome in severe depressive episode.

The DSM-IV-TR definition of the depressive episode is similar in essence to the ICD-10 definition; however there are some differences. The time duration of 2 weeks is the same, but the first set of criteria to be met (the equivalent of criterion B) includes only the first two, that is depressed mood and loss of pleasure and not decreased energy, and demands either of them to be present in contrast to ICD which demands two out of three. The list of depressive symptoms of DSM-IV-TR does not include "loss of confidence or self esteem" and demands five out of a total of nine to be present. There is a definition for "mild" (up to 6 symptoms) but the definition of "moderate" and "severe" episodes are based rather on global disability. Most criteria include a more explicit time and intensity description, e.g., "nearly every day." ICD-10 demands symptoms do not fulfill the diagnosis of a manic/hypomanic episode while DSM-IV-TR demands the same for a mixed episode, but in essence it is the exactly the same. DSM-IV-TR includes the need of a functional impairment and that symptoms are not better accounted by bereavement. Both systems accept the possibility of the presence of mood congruent or incongruent psychotic symptoms; however while the ICD-10 implies that specific psychotic symptoms are more or less pathognomonic of a schizophrenia-like psychosis (like hallucinations giving a running commentary), the DSM-IV-TR accepts all kind of psychotic experiences in the frame of a mood episode. This creates a profound difference in the way the two systems define the boundary between psychotic mood disorder and schizoaffective disorder, and define the latter in a very different way. Another important difference between the two systems is that the ICD-10 defines the "somatic syndrome" while the DSM-IV-TR the "melancholic features." Both definitions are an attempt to include an "endogenous/melancholic-like" subgroup in the classification. It seems that the DSM-IV-TR definition is closer to this, while the ICD-10 definition includes too many anxiety and non-specific symptoms. Also the DSM-IV-TR includes the "atypical features" on the basis of mood reactivity, interpersonal rejection sensitivity and reversed neurovegatative symptoms. It seems that the DSM approach has higher reliability (Fountoulakis et al. 1999). Also catatonic features and postpartum onset are distinct specifiers for DSM.

B. MANIC EPISODE

F30.0: **Hypomania**

A. The mood is elevated or irritable to a degree that is definitely abnormal for the individual concerned and sustained for at least 4 consecutive days.

B. At least three of the following signs must be present, leading to some interference with personal functioning in daily living:

(1) increased activity or physical restlessness;

(2) increased talkativeness;

(3) distractibility or difficulty in concentration;

(4) decreased need for sleep;

(5) increased sexual energy;

(6) mild overspending, or other types of reckless or irresponsible behavior;

(7) increased sociability or overfamiliarity.

C. The episode does not meet the criteria for mania (F30.1 and F30.2), bipolar affective disorder (F31._), depressive episode (F32._), cyclothymia (F34.0), or anorexia nervosa (F50.0).

D. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00-F09).

F30.1: **Mania without psychotic symptoms**

A. Mood must be predominantly elevated, expansive, or irritable, and definitely abnormal for the individual concerned. The mood change must be prominent and sustained for at least 1 week (unless it is severe enough to require hospital admission).

B. At least three of the following signs must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living:

(1) increased activity or physical restlessness;

(2) increased talkativeness ("pressure of speech");

(3) flight of ideas or the subjective experience of thoughts racing;

(4) loss of normal social inhibitions, resulting in behavior that is inappropriate to the circumstances;

(5) decreased need for sleep;

(6) inflated self-esteem or grandiosity;

(7) distractibility or constant changes in activity or plans;

(8) behavior that is foolhardy or reckless and whose risks the individual does not recognize, e.g., spending sprees, foolish enterprises, reckless driving;

(9) marked sexual energy or sexual indiscretions.

C. There are no hallucinations or delusions, although perceptual disorders may occur (e.g., subjective hyperacusis, appreciation of colors as especially vivid).

D. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00-F09).

F30.2: **Mania with psychotic symptoms**

A. The episode meets the criteria for mania without psychotic symptoms with the exception of criterion C.

B. The episode does not simultaneously meet the criteria for schizophrenia (F20.0-F20.3) or schizoaffective disorder, manic type (F25.0).

C. Delusions or hallucinations are present, other than those listed as typically schizophrenic in criterion G1(1)b, c and d for F20.0-F20.3 (i.e., delusions other than those that are completely impossible or culturally inappropriate, and hallucinations that are not in the third person or giving a running commentary). The commonest examples are those with grandiose, self-referential, erotic, or persecutory content.

D. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00-F09).

F30.20: **With mood-congruent psychotic symptoms** (such as grandiose delusions or voices telling the individual that he or she has superhuman powers)

F30.21: **With mood-incongruent psychotic symptoms** (such as voices speaking to the individual about affectively neutral topics, or delusions of reference or persecution)

F30.8: **Other manic episodes**

F30.9: **Manic episode, unspecified**

The DSM-IV-TR definition of the manic episode does not include a specific criterion for sexual behavior and condenses three ICD-10 criteria (#1, 4 and 8) into two. In essence the definitions are almost identical also requiring the same time duration. However, while in the ICD-10 the definition of hypomania requires a different set of criteria, in DSM-IV-TR hypomania differs from mania only in the duration which is at least 4 days and in the criterion suggesting a milder impairment in comparison to mania. Maybe the ICD-10 definition includes some cases which could be subthreshold for DSM-IV-TR. The DSM-IV-TR includes criteria concerning the impairment severity and suggests that hypomania is a milder condition which however, is clearly different from the normal condition of the person and is observable by others. It also includes a note that hypomania caused by any somatic antidepressant treatment should not count towards the diagnosis of a bipolar disorder.

C. MIXED EPISODE

F38.0: **Mixed affective episode**

A. The episode is characterized by either a mixture or a rapid alternation (i.e., within a few hours) of hypomanic, manic, and depressive symptoms.

B. Both manic and depressive symptoms must be prominent most of the time during a period of at least 2 weeks.

The DSM-IV-TR definition demands the patient fulfills for at least 1 week the criteria both for a major depressive and a manic episode, thus this definition is far more rigid. Taking into account the fact that a significant number of patients might fulfill the ICD-10 criteria for mixed episode, but not the respective DSM-IV-TR definition, this difference in classification could make classifications by the two systems to deviate significantly. Both systems classify "ultra-rapid cycling" as mixed episodes.

On the basis of the existence or not of hypomanic, manic, depressive and mixed episodes and accompanying features and longitudinal course, the ICD-10 recognizes the following disorders:

D. DISORDERS

F33: **Recurrent depressive disorder**

- current episode mild, with/without somatic syndrome
- current episode moderate, with/without somatic syndrome
- current episode severe with/without mood-congruent/incongruent psychotic symptoms
- currently in remission
- Other recurrent depressive disorders
- Recurrent depressive disorder, unspecified

F31: **Bipolar affective disorder**

- current episode hypomanic
- current episode manic with/without mood-congruent/incongruent psychotic symptoms
- current episode moderate or mild depression with/without somatic syndrome
- current episode severe depression with/without mood-congruent/incongruent psychotic symptoms
- current episode mixed
- currently in remission
- Other bipolar affective disorders
- Bipolar affective disorder, unspecified

F34.0: **Cyclothymia**

A. There must have been a period of at least 2 years of instability of mood involving several periods of both depression and hypomania, with or without intervening periods of normal mood.

B. None of the manifestations of depression or hypomania during such a 2-year period should be sufficiently severe or long-lasting to meet criteria for manic episode or depressive episode (moderate or severe); however, manic or depressive episode(s) may have occurred before, or may develop after, such a period of persistent mood instability.

C. During at least some of the periods of depression at least three of the following should be present:

(1) reduced energy or activity;

(2) insomnia;

(3) loss of self-confidence or feelings of inadequacy;

(4) difficulty in concentrating;

(5) social withdrawal;

(6) loss of interest in or enjoyment of sex and other pleasurable activities;

(7) reduced talkativeness;

(8) pessimism about the future or brooding over the past.

D. During at least some of the periods of mood elevation at least three of the following should be present:

(1) increased energy or activity;

(2) decreased need for sleep;

(3) inflated self-esteem;

(4) sharpened or unusually creative thinking;

(5) increased gregariousness;

(6) increased talkativeness or wittiness;

(7) increased interest and involvement in sexual and other pleasurable activities;

(8) overoptimism or exaggeration of past achievements.

Note. If desired, time of onset may be specified as early (in late teenage or the 20s) or late (usually between age 30 and 50 years, following an affective episode).

F34.1: **Dysthymia**

A. There must be a period of at least 2 years of constant or constantly recurring depressed mood. Intervening periods of normal mood rarely last for longer than a few weeks, and there are no episodes of hypomania.

B. None, or very few, of the individual episodes of depression within such a 2-year period should be sufficiently severe or long-lasting to meet the criteria for recurrent mild depressive disorder (F33.0).

C. During at least some of the periods of depression at least three of the following should be present:

(1) reduced energy or activity;

(2) insomnia;

(3) loss of self-confidence or feelings of inadequacy;

(4) difficulty in concentrating;

(5) frequent tearfulness; (6) loss of interest in or enjoyment of sex and other pleasurable activities;

(7) feeling of hopelessness or despair;

(8) a perceived inability to cope with the routine responsibilities of everyday life;

(9) pessimism about the future or brooding over the past;

(10) social withdrawal;

(11) reduced talkativeness.

Note. If desired, time of onset may be specified as early (in late teenage or the 20s) or late (usually between age 30 and 50 years, following an affective episode).

F34.8: **Other persistent mood [affective] disorders**

This is a residual category for persistent affective disorders that are not sufficiently severe or long-lasting to fulfill the criteria for cyclothymia (F34.0) or dysthymia (F34.1) but that are nevertheless clinically significant. Some types of depression previously called "neurotic" are

included here, provided that they do not meet the criteria for either cyclothymia (F34.0) or dysthymia (F34.1) or for depressive episode of mild (F32.0) or moderate (F32.1) severity.

F34.9: **Persistent mood [affective] disorder, unspecified**

F38: **Other mood [affective] disorders**

There are so many possible disorders that could be listed under F38 that no attempt has been made to specify criteria, except for mixed affective episode (F38.00) and recurrent brief depressive disorder (F38.10). Investigators requiring criteria more exact than those available in Clinical descriptions and diagnostic guidelines should construct them according to the requirements of their studies.

F38.10: **Recurrent brief depressive disorder**

A. The disorder meets the symptomatic criteria for mild (F32.0), moderate (F32.1), or severe (F32.2) depressive episode.

B. The depressive episodes have occurred about once a month over the past year.

C. The individual episodes last less than 2 weeks (typically 2–3 days).

D. The episodes do not occur solely in relation to the menstrual cycle.

F38.8: **Other specified mood [affective] disorders**

This is a residual category for affective disorders that do not meet the criteria for any other categories F30-F38.1 above.

There are significant differences in the way the two systems conceptualize bipolar illness apart from the differences that occur because of different definitions of mood episodes. The DSM-IV-TR separates Bipolar I (which includes manic episodes) and Bipolar II (which includes hypomanic but not manic episodes) disorders on the base of the longitudinal history of the disorder. On the contrary, the ICD-10 distinguishes them only concerning the "current episode" irrespective of past episodes. The greatest difference concerning cyclothymia is that ICD-10 demands the presence of 3 out of 8 depressive or manic symptoms during the downs and up, while the DSM-IV-TR refers only to depressive and hypomanic symptoms from the list of criteria for major depressive and hypomanic episodes without any threshold. On the contrary the separate lists of symptoms criteria suggested by the ICD-10 differ significantly from the respected list for depressive episodes and hypomanic episodes and thus eventually the definitions of cyclothymia of the two classification systems differ significantly. The definition of DSM-IV-TR concerning dysthymia differs significantly from that of ICD-10 since it demands the presence of 2 out of 6 criteria in comparison to 3 out of 11 for ICD-10. The DSM-IV-TR criteria include appetite and weight changes and hypersomnia and not only insomnia. The ICD-IV-TR largely duplicates criteria although depending on the definition overlapping is not complete always (e.g., "depressed" and "frequent tearfulness;" "pessimism" and "hopelessness"). The DSM-IV-TR definition considers dysthymia to be a chronic mild form of depression while the ICD-10 stresses the cognitive and interpersonal impairment.

Classification of mood disorders due to a somatic disease or substance abuse:

F00-F09: **Organic, including symptomatic mental disorders**

F06.3: **Organic mood (affective) disorder**

F06.30: **Organic manic disorder**

F06.31: **Organic bipolar disorder**

F06.32: **Organic depressive disorder**

F06.33: **Organic mixed affective disorder**

F06.6: **Organic emotionally labile (asthenic) disorder**

F10-F19: **Mental and behavioural disorders due to psychoactive substance use**

F1x.54: **Predominantly depressive symptoms**

F1x.55: **Predominantly manic symptoms**

F1x.56: **Mixed**

Assessment

Mood disorders should be differentially diagnosed from a number of other morbid conditions, both psychiatric and non-psychiatric.

Several mental disorders including alcohol and substance use disorders, normal bereavement, depression in the frame of schizophrenia, anxiety disorders, personality disorders, dementia and a variety of general medical conditions that cause syndromes similar to depression should be differentiated from mood disorders. Also several drugs used for the treatment for a number of diseases might also cause depression. In general the prevailing opinion is that a missed diagnosis of mood disorder in favor of another mental diagnosis may mean that the patients does not receive proper treatment, which has serious consequences.

Maybe the most important differential diagnosis should be made between mood and personality disorders. Since the state dependency of most personality features is well documented (Grilo et al. 2004; Grilo et al. 2005; Gunderson et al. 2004; McGlashan, 1986; McGlashan et al. 2005; Morey et al. 2004; Stone, 1993, 2005; Warner et al. 2004), clinicians should avoid putting this diagnosis in patients with an active mood disorder, even in cases this mood disorder is subthreshold. A dangerous stereotypical thinking leads clinicians to suggest that because a patient does not respond adequately to usual treatment the disorder is personality-based. This is especially problematic concerning subthreshold or non-classic mixed clinical pictures which are relatively refractory to treatment and cause despair to the therapist.

Normal bereavement appears normally in persons experiencing the loss of a significant other and consists of several depressive symptoms during the first 1-2 years after the loss. But only around 5% will eventually progress to a depressive disorder. Normal bereavement is generally contrasted with depression because reactivity to the environmental stimuli is preserved, the disability if any is mild and no severe psychopathology (delusions or hallucination or true suicidal ideation) is present.

Anxiety symptoms commonly occur in mood patients, including panic attacks, fears, and obsessions. Longitudinal data suggest that although the depressive symptoms tend to remit by passing the time, the anxiety symptoms persist. Because anxiety disorders rarely appear after the age of 40 for the first time, a late appearance of significant anxiety should be

considered to be a sign of depression. Transient and periodic monosymptomatic phobic and obsessional states that do not fulfill criteria for a formal disorder as conceptualized in either classification system should also be considered as reflecting an underlying mood disorder and should be treated accordingly.

Somatic complaints especially in depression might also reflect an underlying physical illness rather than a somatization mechanism. The somatic disorders most commonly related to depression are Multiple Sclerosis, Parkinson's disease, head trauma, epilepsy, sleep apnea, cerebral tumors, vascular encephalopathy, chronic fatigue syndrome, some collagen disorders like rheumatoid arthritis and lupus erythematosus and various neoplastic conditions like abdominal malignancies (especially in the pancreas) and disseminated carcinomatosis. Also there is a number of abnormal endocrine conditions including hypo- and hyperthyroidism, hyperparathyroidism, hypopituitarism, Addison's disease, Cushing's disease and diabetes mellitus, several infections like general paresis (tertiary syphilis), toxoplasmosis, influenza, viral pneumonia, viral hepatitis, infectious mononucleosis and AIDS, and nutritional conditions like pellagra and pernicious anemia.

A number of pharmacological agents used for the treatment of various diseases could cause depression or a depressive-like condition. These include a-methyldopa, anticholinesterase insecticides, cimetidine, cycloserine, indomethacin, mercury, phenothiazine antipsychotic drugs, reserpine, steroidal contraceptives, thallium, vinblastine and vincristine Withdrawal from agents like amphetamine, alcohol or sedative-hypnotics could also be the cause of depression.

In geriatric patients the differentiation between depressive pseudodementia and degenerative dementia is vital and is done by the neuropsychological profile of the patient as well as from the clinical course which in pseudodementia cases includes an acute onset without prior cognitive disorder, a personal or family history of affective illness, circumscribed memory deficits and an unstable cognitive dysfunction that can be reversed with proper coaching.

The need for the differential diagnosis of mood disorders from the above mentioned conditions makes important for the clinician to obtain a variety of laboratory examination data including standard blood and biochemical tests, EEG, ECG, thyroid function tests and in depending on availability and cost even brain MRI and in late onset cases indices assessing malignancy.

There are a large number of neuropsychological and psychometric tools available for the assessment of mood disorders and the clinician can choose which to use on the basis of his training and specific needs. However, a basic list includes the following tools:

Psychometric Tools

- Visual Analogue Scale (Rosenthal, Goldfarb, Carlson, Sagi, & Balaban, 1987): This is a very simple method, according to which, the examiner or the patient himself is asked to determine the quantity of the symptomatology on a bar 100 mm in length. One end of the bar is defined as "lack of depression" (0 mm) and the opposite one as "profound depression" (100 mm). The distance from the beginning (0 mm) is considered as the "degree" of depression. This method is has been in existence since 1921. A positive relationship between the subject's ratings, the examiners' opinion, and the score on the Beck Depression Inventory is reported. Today, it is considered somewhat outdated and not suitable for research purposes.

- Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960): This is the most widely known and used scale worldwide. It is examiner-rated. The basic scale includes 17 items, some of them assessing somatic symptoms, other assess anxiety or vegetative function and others could be contaminated by medication side effects. Therefore although it is a comprehensive scale, its use of this scale in somatic patients or the elderly patients has some limitations. It also under-assesses atypical depressive patients.
- Beck Depression Inventory (BDI-I) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961): This is a widely used self-report scale that measures the thought content, or cognitive aspect of depression. It includes 21 items. Its properties when used in somatic patients or the elderly are less well known. A revised version (BDI-II) (Beck, Steer, Ball, & Ranieri, 1996) which is adjusted to modern classification is also available.
- Zung Depression Rating Scale (ZDRS) (Zung, 1965): This is an old self-report scale which reflects an older concept of depression that dominated during the 60s, and might not produce reliable and valid results in somatic patients and geriatric populations. It also under-assesses atypical depressive patients.
- Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979): This instrument was the product of the need for scales with high sensitivity to changes produced by antidepressant medication. It is rated by an examiner. As a result, it includes only 10 items and almost no "somatic" symptomatology. A significant drawback of this scale is that its content is restricted to those symptoms responsive to medication at the time of the design of the scale, and therefore it does not represent a global assessment of depression. Another drawback is that it was developed for use in younger and somatically healthy patients. The content and method of development of the scale might make its application in somatic patients and elderly individuals problematic and its application in this population may lead to erroneous conclusions.
- Geriatric Depression Scale (GDS) (Yesavage et al. 1982): It is the first scale especially designed for use in elderly populations. It is a self-report scale however, sometimes it is necessary to administer it through an interviewer. It exists in a 30-item and a 15-item form. It focuses mainly on the psychological concern of the patient and the way he/she perceives life, avoiding the assessment of somatic complaints.
- Center for Epidemiological Studies-Depression Scale (CES-D) (Radloff, 1977): It is a self-report instrument and one of the most widely used. It seems that it is this scale is least affected by somatic disorders and handicaps. It consists of 20 items. The validity of the CES-D might be compromised when used with somatic patients or elderly individuals, and modifications for its use in this population has been recommended.
- Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978): The YMRS is an 11-item scale used to assess the severity of mania in patients with a diagnosis of bipolar disorder. It takes 15-30 minutes to complete by a trained examiner. It is a reliable easy to use and simple tool, widely used. Some 4 items have double-rating which can lead to questions of reliability.
- The Bech-Rafaelsen Mania Rating Scale (MRS) (Bech, Rafaelsen, Kramp, & Bolwig, 1978): It consists of 11 items and assesses the severity of mania in bipolar patients. It is rated by an examiner.
- General Assessment of Functioning) (GAF): This is a scale introduced by the DSM classification system, that assesses global functioning in the psychological, family, social and occupational spheres and attempts to localize it on a continuum from 0 (full decline of functioning, the patient is dangerous to self or others) to 100 (supreme level of functioning).

It shares many characteristics with the visual analog scale, and represents a non-specific way to quantify everyday functioning, but with low reliability and accuracy.
- General Assessment of Relational Functioning (GARF): It can be used to assess the patient's family or the general environment in which he/she lives.
- Social and Occupational Functioning Assessment Scale (SOFAS): This is a scale for the assessment of functioning in work place and in social situations. Both GARF and SOFAS are introduced by DSM-IV, and share characteristics with GAF. Their major difference is that they have a restricted field of functioning to assess.
- Clinical Global Impression (CGI): This is a group of simple scales assessing symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders. They include the Clinical Global Impression - Severity scale (CGI-S) which is a 7-point scale, the Clinical Global Impression - Improvement scale (CGI-I) which is a 7 point scale and the Clinical Global Impression - Efficacy Index which is a 4 point X 4 point rating scale
- TEMPS-A (Akiskal, Akiskal, Haykal, Manning, & Connor, 2005), NEO-PI (Costa & McCrae, 1997), TCI (Cloninger, Svrakic, & Przybeck, 1993) and the MMPI-2 (Butcher, Graham, & Fowler, 1991): They are self-report questionnaires that assess temperament, character and personality

The literature suggests there is no significant difference among the various self-administered instruments assessing depression in terms of performance and overall sensitivity is around 84% and specificity around 72% (Fountoulakis, Bech et al. 2007; Mulrow et al. 1995).

Neuropsychological Tools

The assessment of neurocognitive function is very important especially for psychogeriatric patients even in cases without observable symptoms or signs of "organic" disorder or dementia. Scales for rapid screening of cognitive disorder are the following:

- Mini Mental Status Exam-(MMSE) (Folstein, Folstein, & McHugh, 1975): It is a brief mental status examination designed to quantify cognitive status by assessing performance on the following cognitive domains: orientation, language, calculation, memory and visuospatial reproduction thus providing a brief measure of global cognitive functioning.
- The Cambridge Cognitive Examination For The Elderly-(CAMDEX) (Roth et al. 1986): It includes a large number of items covering almost every aspect of the patient's medical history as well as his/her family medical history. It also includes evaluation of the patients' current condition concerning both physical and mental health. Sixty-eight of these items constitute the CAMCOG scale, which is the part of CAMDEX examining the patient's cognitive functions. The MMSE score is simultaneously obtained. CAMCOG includes eleven subscales. Each one evaluates a "different" cognitive function of the patient: Orientation, Language/Comprehension, Language/Expression, Remote Memory, Recent Memory, Learning, Attention, Praxis, Calculations, Abstract Thinking and Perception.
- Weschler Memory Scale-Revised (D'Elia, Satz, & Schretlen, 1989) Maybe the most global and comprehensive scale for the assessment of memory. Its greatest drawback is that it is time consuming. It includes testing of Personal and current information, Orientation, Mental Control, Logical Memory, Digits forward and backward, Visual reproduction and Associated learning.
- Weschler Adult Intelligence Scale - Revised (WAIS-R): The WAIS-R gives a global Intelligence Quotient (IQ) and also two subscales: verbal and performance.

- Clock Drawing Test (Sunderland et al. 1989): This is a simple test which demands the patient to draw a clock. It can be used as a screening tool especially for dementia. The test requires multiple cognitive functions to co-operate.
- Verbal Fluency Test : The test demands the patient to name as many objects and animals is able to within a time frame of 1 minute.
- Trail Making Test (Reitan, 1971): The first form of is test demands the patient to trail the sequence of numbers put at random places on paper by using a pencil, while the second form demands to alternate between numbers and letters randomly put on paper. The time needed to fulfill each of the two tasks is recorded. The test is an assessment of general mental function.

3.0.3 Pathogenesis

Today most mood disorders experts agree that mood disorders have both endogenous and exogenous components and in most patients they are both present. After the historical dualism suggested by Rene Descartes in the 17th century, only as recent as the early 20th century Adolf Meyer used the term "psychobiology" to emphasize that psychological and biological factors interact in the development of mental disorders. The bio-psycho-social model has been proposed by Engel (Engel, 1977, 1980) and provides a non specific but inclusive theoretical framework in order to host all variables suggested by various approaches to cause depression.

Social Stressors

Although lay people and much of psychological theories attribute mood disorders to adverse life events, there are several studies which dispute the role stressful life events play in the development or the course of depression (Harkness & Luther, 2001; E. Paykel, Rao, & Taylor, 1984). But the sensitization of stress-responsive neurobiological systems as a possible consequence of early adverse experience has been more solidly implicated in the pathophysiology of mood and anxiety disorders. A history of childhood abuse per se may be related to increased neuroendocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood (Heim et al. 2002). In this frame, depressed patients were reported to have higher perceptions of day-to-day stressors (hassles), reduced perception of uplifting events, excessive reliance on emotion-focused coping strategies, and diminished quality of life in comparison to controls. Among depressed patients the hassles, coping styles and some elements of quality of life were related to symptom severity, as well as treatment-resistance (Ravindran, Matheson, Griffiths, Merali, & Anisman, 2002). The question that arises is whether this is a true fact or these patients (which have higher personality psychopathology and interpersonal rejection sensitivity) tend to over-report life events (Fountoulakis, Iacovides, Kaprinis, & Kaprinis, 2006).

Thus, many authors insist that psychosocial factors are relatively unimportant in the subsequent course of severe and recurrent depressions, in contrast to their contribution to onset of such depressions and subsequent outcome of milder depressions (Paykel, Cooper, Ramana, & Hayhurst, 1996; Thomson & Hendrie, 1972).

Psychological Models of Mood Disorders

There are a number of psychological models proposed during the last 100 years to explain the pathogenesis of depression. The most important are the following:

1. Aggression-Turned-Inward Model: It has been proposed by Sigmund Freud and Karl Abraham on the basis of a "metaphor" from physics to psychology ("hydraulic mind"). According to this model, during the oral phase (that is, during the 12-18th months of life) disturbances in the relationship between the infant and the mother establish a vulnerability to develop depression. Then during the adult life, a real or imaginary loss leads to depression as the result of aggressive impulses turned inward and directed against the ambivalently loved internalized object which had been lost. The aim of that turned-inwards aggression was supposed to be the punishment of the love object which fails to fulfill the patient's need to be loved. It is therefore accompanied by guilt which could lead to suicidal behavior. Later other authors proposed somewhat different versions of this model. The drawbacks of this model include that it represents a relatively closed circuit independent of the outside world, while the clinical fact is that many depressed patients openly express anger and hostility against others which is reduced after treatment, and that there are no evidence supporting the concept that expressing anger outwards has a therapeutic effect in the treatment of clinical depression behavior

2. Object Loss: The term refers to traumatic separation from significant objects of attachment. However, according to empirical research data, only a minority of no more than 10% of people experiencing bereavement will eventually manifest clinical depression. Thus the model includes two steps; an early one which includes significant loss during childhood thus creating a vulnerability which during the second step, that is significant loss during adult life, leads to clinical depression. This model fits better the data in comparison to the aggression-turned-inward and has some support by studies on primates although the latter point to a broad psychopathology rather than specifically depression.

3. Loss of Self-Esteem: Depression is considered to originate from the inability of the ego to give up unattainable goals and ideals resulting in a collapse of self-esteem. This model suggests that the narcissistic injury that destroys the patient's self-esteem comes from the internalized values of the ego rather than the hydraulic pressure deriving from the id as proposed by the aggression-turned-inward model. In this frame the loss of self-esteem has a sociocultural and existential dimension and thus this theory is testable to a significant extent. The drawback of this theory is that both persons with low and high self esteem can develop depression or mania without any significant differences among them.

4. Cognitive Model: The cognitive model was developed by Aaron Beck and suggests that thinking in a negative way is the core of clinical depression. According to this, depression is conceptualized in the frame of the "cognitive triad." This triad proposes that patients conceive the self, the environment and the future in a negative depressive way (helplessness, negative and hopelessness). In the core there seems to be bias of the person in the way of thinking and interpreting which results in a profound negative attributional style (mental schemata) which is considered to be global, internal, and stable. The bias in the way of thinking is because of overgeneralization, magnification of negative events with a simultaneous minimization of positive events, arbitrary inference, and selective abstraction. Systematic errors in thinking, allow the persistence of negative schemas despite contradictory evidence.

The major drawback of this model is the fact that it is based on retrospective observations of depressed patients, thus the negative triad could be simply subclinical manifestations of depression and not the cause of it. The major advantage is that it led to the first testable and practical psychotherapeutic approach which seems to be effective in a specific subgroup of patients.

5. Learned Helplessness Model: This model is based on animal experiments and proposes that the depressive attitude is learned during past situations in which the person was not able to terminate or avoid undesirable or traumatic events. However, it seems that the learned helplessness paradigm is more general and refers to a broader mental condition (e.g, behavior, posttraumatic stress disorder etc.). It seems that past events could shape a personality profile which includes passivity, lack of hostility, and self-blame. However, this line of thinking could lead to the notion that depression and the behavior accompanying it should be considered to be a result of a masochistic lifestyle with manipulative behavioral patterns in order to handle interpersonal issues. Even more, recent animal research has implicated the importance of genetic factors in the vulnerability to learning to behave helplessly.

6. Depression and Reinforcement: According to the reinforcement the behavior characteristic of depression develop because of a lack of appropriate rewards and with receipt of non-contingent rewards. This theory bridges personality, low self esteem and learned helplessness with the human social environment; however it seems more appropriate for the interpretation of social issues than clinical depression. A psychotherapeutic approach aiming to improve the patient's social skills is based on this theory.

7. Psychological theories of Mania: Most theories view manic symptoms as a defense against an underlying depression with the use of a number of defense mechanisms like omnipotence, denial, idealization, and contempt. In this frame, the euphoric state of the patient is understood as a tendency to extinguish any unpleasant aspects of reality and to disregard for the problems of reality, even if the situation is tragic. Thus mixed episodes are easily psychodynamically understood, since as manic elements seen in depressed patients are considered to be defenses.

Biological Models of Mood Disorders

Data coming from animal experiments and models implicate the limbic-diencephalic brain in mood disorders and more specifically neurons containing serotonin and noradrenaline. Historically the monoamine deficiency hypothesis is based on data from the study of the cerebrospinal fluid (CSF) metabolites. According to this theory, there is a monoamine deficiency, especially norepinephrine (NE), in depression. Later, studies illustrated that this theory should also include serotonin (5-HT), leading to a broader theory regarding neurotransmission disorder in Central Nervous System (CNS) (Maas, 1975; Schildkraut, 1965; Van Praag & Leijnse, 1963). Later, the cholinergic-noradrenergic imbalance hypothesis (Janowsky, el-Yousef, Davis, & Sekerke, 1972) included acetycloline in a broader model for mood disorders. More complex models include state changes (depending on the polarity of the mood episode) in the excitatory amino acid function in specific areas of the cortex (Fountoulakis, Giannakopoulos, Kovari, & Bouras, 2008).

However, in spite of decades of extensive research there is no definite proof for either a deficiency or an excess of either the quantity or the overall functioning of biogenic amines in specific brain structures. Even when these abnormalities were documented, it has been shown that they are neither necessary nor sufficient for the occurrence of mood disorders. In contrast, it seems that the neurotransmitter disorders recognized until today refer to a broader behavioral dysfunction which includes behavioral disinhibition, obsessive-compulsive symptoms, anxiety, eating disorders and substance and alcohol abuse as well as personality disorders. This is not peculiar since most classic animal models are in essence post-traumatic stress models and most biological psychoendocrinological markers are markers of stress-related somatic reactions. Recent research explores disturbances at the level of second messengers and close to DNA function with variable success but no definite conclusions.

A number of biological markers have been developed so far but no one is proved so far strong enough for use in clinical practice. The dexamethasone-suppression test (DST) has been widely used for the study of hypothalamus-pituitary-adrenal (HPA) axis disorders in patients with depression (Evans & Golden, 1987; Green & Kane, 1983; Stokes et al. 1984). It requires the oral administration of 1mg dexamethasone (a synthetic glucocorticoid) at 23:00 on day 1 and the assessment of cortisol levels at the same time, at 08:00, 16:00, and at 23:00 on day 2. A cortisol value of 5?g/dl, in at least one measurement in day 2, is considered to be the cut-off point between normal (suppressors) and pathological (non-suppressors). Longer protocols requiring higher dosage for dexamethasone and a 24 hour long assessment have also been suggested. The test presents a 67% sensitivity and 96% specificity in the diagnosis of melancholy in psychiatric inpatients. The results of the up to date research efforts report that DST presents results that are probably related with the severity of depression and the patient's family history. Other psychoendocrinological markers are the TRH Stimulation Test (blunted thyroid-stimulating hormone response to thyrotropin-releasing hormone) (Kendler, Thornton, & Gardner, 2000; Musselman & Nemeroff, 1996), the fluramine and d-fenfluramine challenge tests which (Di Renzo & Amoroso, 1989; Fessler, Deyo, Meltzer, & Miller, 1984; Garattini, Mennini, & Samanin, 1987, 1989; Invernissi, Berettera, Garattini, & Samanin, 1986; Ouattrone, Tedeschi, Aguglia, & Scopacasa, 1983; Quattrone, Schettini, & DiRenzo, 1979; Rowland & Carlton, 1986; Siever & Murphy, 1984; Zarifian, 1993) are supposed to reflect central serotonin activity (administration of 30 mg of the d-fenfluramine orally and measurement of prolactin plasma levels at the baseline and 60?, 120?, 180?, 240? and 300? after the administration), blunted growth hormone (GH) response to the a2-adrenergic receptor agonist clonidine (an index of noradrenergic dysregulation) and others. A non-endocrinological marker is based on EEG and concerns the observation that depressed patients are phase advanced in many biological rhythms, especially concerning the latency to the first rapid eye movement in sleep (shortened REM latency) (Kupfer, 1976).

A possible comprehensive model could suggest that mood patients have a deficit in the adequate mobilization of neurotransmitters when facing continued or repeated stress, and as a result, through a "kindling" effect (Kendler et al. 2000; Post, Weiss, & Pert, 1984, 1988; Post & Weiss, 1989; Post, Susan, & Weiss, 1992; Post & Silberstein, 1994; Post & Weiss, 1998), the mood change is intense, prolonged and not self-limited, and tends to be triggered by progressively unimportant events and finally automatically. Thus it is expected that an early application of treatment with antidepressants and psychotherapy could prevent neuroplastic changes and the long term worsening of the clinical course.

The data from family and twin studies argue strongly for the familial nature of mood disorders (Kendler, Pedersen, Johnson, Neale, & Mathe, 1993; Sadovnick et al. 1994). However, so far the mode of genetic transmission remains elusive. Several studies have focused on a functional polymorphism in the promoter region of the serotonin transporter serotonin transporter gene (HTTLPR) which is supposed to moderate the influence of stressful life events on depression and the brain derived neurotrophic factor (BDNF) which is supposed to exert a prophylactic effect against neuronal toxicity induced by stress (Belmaker & Agam, 2008; Caspi et al. 2003; Kato, 2007). The most possible model is a multifactorial-threshold model. The twin data suggest that genes account for 50-70% of the etiology of mood disorders.

3.0.4 Treatment

Mood disorders are not only formally distinguished into two major groups, that is unipolar and bipolar mood disorder, but also treatment differs between them. Even within the unipolar group different subcategories exist, that demand somewhat different treatment. Psychotherapy as monotherapy is generally reserved for milder cases while antidepressants are first choice for moderate to severe cases. Patients with psychotic features need adding antipsychotic. Bipolar patients need a core treatment with the so-called mood stabilizers and depending on the episode and the state of the clinical picture additional agents can be used.

Treatment is artificially separated into acute face treatment and maintenance. During the acute-phase the therapist should decide where the patient should be treated (e.g., outpatient, inpatient, day hospital etc). The decision is based on the assessment of issues like the risk of suicide, the patient's insight, comorbidity, severity of impairment and the psychosocial support available. As a general rule, patients who respond to acute-phase treatment receive a similar treatment during the maintenance phase. During that phase, medication should be kept at the same dosage if possible.

Unipolar Mood Disorders

Psychotherapy

The first kind of available treatment for mood disorders was psychotherapy. Some kind of psychosocial, moral or psychotherapeutic intervention was available since antiquity; however only during the 20th century psychotherapy was systematically developed as a formal treatment.

A variety of psychotherapies are today available and to some extend have a proven efficacy in the treatment of mood disorders. Although there are still psychoanalytical and psychodynamic-oriented approaches, today most professionals prefer the more pragmatic, short term and focused approaches of behavioral or cognitive therapy or utilize an eclectic approach.

The evidence so far altogether seems enough to support the efficacy of psychotherapeutic strategies in mild and moderate depression but not in more severe cases. However, the evaluation of psychotherapies is not as good as that of antidepressants. Most psychotherapies,

especially the psychodynamically oriented are not possible to be tested scientifically while the practical ones like cognitive and behavioral have not been tested under placebo conditions and it is doubtful this is possible (Cuijpers, van Straten, & Warmerdam, 2007a, 2007b; Hegerl, Plattner, & Moller, 2004; Paykel, 2007). Thus important questions remain concerning the use and usefulness of psychotherapy in mood disorders. Some authors suggest psychotherapies should be considered as equal alternatives to medication especially under the warning that antidepressants and maybe anticonvulsants provoke suicidality; however there are reports suggesting that even psychotherapy can also evoke suicidal thoughts (Moller, 1992).

There are no established clinical predictors to guide the choice of a specific kind of psychotherapy for the individual patient.

- Interpersonal therapy (ITP): It was developed by Gerald Klerman and Myrna Weissman and its basic concepts include accepting the patient to assume the sick role and focusing on improving the patient's interpersonal functioning. Since depression can cause interpersonal problems, and vice versa interpersonal problems can precipitate depression, IPT focuses on solving these problems. It is a short-term psychotherapy (12-16 weekly sessions) and the therapeutic goals include reducing depressive symptoms (by an educational approach), improving self-esteem and helping the patient to develop more-effective copying strategies concerning social and interpersonal relations.
- Cognitive-behavioral therapy (CBT) was developed by Aaron Beck and is based on cognitive and behavioral psychology and the cognitive theory on the etiopathogenesis of depression. It aims at changing the way a person thinks and in this way it alleviates depression and prevents recurrence. It utilizes didactic methods and cognitive and behavioral techniques. The patient is encouraged to identify and challenge negative conditions, develop alternative, and more flexible cognitive schemas, and exhibit new behavioral patterns. It is a short-term, structured therapy and demands the active participation of the patient.
- The Behavioral therapy was developed by C.B. Ferster and is based on the work of B.F. Skinner, and the behavioral approach to the etiopathogenesis of depression. It puts the emphasis on the relationship between an observable behavior and the conditions that control or determine it. It also stresses the importance of the role of rewards. A major goal is increasing the frequency of positive reinforcing and decrease negative thus improving social and interpersonal skills.

Biological Treatment

The basis of "biological" treatment is antidepressants although Electro-Convulsive therapy (ECT) and total and partial sleep deprivation are also used in refractory cases. Other therapies which were used in the past and are considered to be effective, like insulin therapy, are no longer in use. The ability of psychiatrists to individualize treatment decisions and choose a specific antidepressant for a specific patient is poor and the choice is largely dependent on adverse effects and comorbid conditions. The therapeutic effect of antidepressants is evident after at least two weeks and therapy should be administered over the course months, or sometimes years.

Antidepressants appeared during the 1950s and the first one was imipramine introduced by Roland Kuhn. Although a variety of mechanisms have been proposed as responsible for the effectiveness of antidepressants, it seems that increasing the serotonin signal in the limbic

system is what eventually survives as a concept. The role of norepinephrine seems to be important too, since its depletion cancels the effectiveness of antidepressants.

The major classes of antidepressant agents are:

- Tricyclics (TCAs): Tricyclic antidepressants are the oldest class of antidepressant drugs. This group includes imipramine, clomipramine, amitryptiline, nortriptyline and desipramine. They act by blocking the reuptake of a number of neurotransmitters including serotonin, norepinephrine and dopamine. Their side effects include increased heart rate, drowsiness, dry mouth, constipation, urinary retention, blurred vision, dizziness, cognitive disorder, confusion, skin rash, weight gain or loss and sexual dysfunction. TCAs can be lethal at overdose (over ten times the therapeutic dosage) usually due to cardiac arrhythmia. However, TCAs are highly effective and are still used especially in severe and refractory depression in spite of the development of newer agents which are safer and with fewer side effects.
- MonoAminOxidase Inhibitors (MAOIs) and Reversible Inhibitors of Monoamineoxidase A (RIMA): reversible" forms affecting only the MAO-A subtype Monoamine oxidase inhibitors (MAOIs) such as phenelzine (Nardil) may be used if other antidepressant medications are ineffective. Because there are potentially fatal interactions between this class of medication and certain foods (particularly those containing Tyramine), red wine, as well as certain drugs, classic MAOIs are rarely prescribed anymore. MAOIs work by blocking the enzyme monoamine oxidase which breaks down the neurotransmitters dopamine, serotonin, and norepinephrine (noradrenaline). MAOIs can be as effective as tricyclic antidepressants, although they can have a higher incidence of dangerous side effects (as a result of inhibition of cytochrome P450 in the liver). A new generation of MAOIs has been introduced; moclobemide (Manerix), known as a reversible inhibitor of monoamine oxidase A (RIMA), acts in a more short-lived and selective manner and does not require a special diet. Additionally, (selegiline) marketed as Emsam in a transdermal form is not a classic MAOI in that at moderate dosages it tends to affect MAO-B which does not require any dietary restrictions. As one of the side effects is weight gain and could be extreme. block the break-down of monoamine neurotransmitters (serotonin and norepinephrine) by inhibiting the enzymes which oxidize them, thus leaving higher levels still active in the brain (synaptic cleft). liver inflammation, heart attack, stroke, and seizures. Serotonin syndrome is a side effect of MAOIs when combined with certain medications
- Selective Serotonin Reuptake Inhibitors (SSRIs): This class of antidepressants appeared in 1988 and includes fluoxetine, paroxetine, sertraline, citalopram and escitalopram and fluvoxamine. It acts presumably by selectively inhibiting the reuptake (by the presynaptic neuron) of serotonin (also known as 5-hydroxytryptamine, or 5-HT). In this way the synaptic levels of 5-HT increase. SSRIs typically have fewer side effects and a more favorable profile in comparison to the TCAs but also in comparison to other classes of antidepressants. Their adverse effects include headache, anxiety, insomnia, nervousness, decreased appetite, decreased libido, drowsiness, dry mouth and serotonin syndrome. There is some data suggesting SSRIs might not be as efficient as other classes especially in more severe cases of depression. Recently the Food and Drug Administration (FDA) has included a Black Box warnings on all SSRIs suggesting an increased like hood for suicidality in children and adolescents who are prescribed these drugs, although

subsequent analysis and ecological studies consider this warning to be exaggerated and in some countries might already have led to an increase of the suicidal rate.

- Serotonin Norepinephrine Reuptake Inhibitors (SNRIs): This is a new group that includes venlafaxine, duloxetine, milnacipram, nefazodone and maybe mirtazapine. These agents inhibit the reuptake of both the 5-HT and norepinephrine. Their side effect profile is more or less similar to that of the SSRIs. After acute discontinuation a withdrawal syndrome could occur. Some data suggest they are as class stronger than the SSRIs.
- Noradrenergic and specific serotonergic antidepressants (NASSAs): This group includes only mirtazapine and mianserin, and suggests it works through the increase of norepinephrine and 5-HT neurotransmission by blocking presynaptic alpha-2 adrenergic receptors while simultaneously minimizes 5-HT related side-effects by blocking specific serotonin receptors. The side effects include the typical SNRI side effects but also include a more pronounced drowsiness, increased appetite, and significant weight gain.
- Norepinephrine (noradrenaline) reuptake inhibitors (NRIs): This group includes reboxetine which exerts its effect via norepinephrine.
- Norepinephrine-dopamine reuptake inhibitors (NDRIs): This group includes bupropion which inhibits the reuptake of dopamine and norepinephrine.

The overall efficacy of antidepressants is well proven (Baghai, Volz, & Moller, 2006; M. Bauer, Whybrow, Angst, Versiani, & Moller, 2002a, 2002b; Bauer et al. 2007) and although recent meta-analysis question their true clinical usefulness (Kirsch et al. 2008), antidepressants constitute the only rigorously tested therapy against depression and their clinical utility is the only one solidly proven (Nutt & Malizia, 2008; Nutt & Sharpe, 2008).

Apart from antidepressants, other classes of psychotropic agents could be used to treat the constellation of symptoms that accompany depression as well as comorbid conditions. The most often used agents are anxiolytics, tranquillizers and sedatives. Usually benzodiazepines serve this role; however they induce tolerance and dependence. The alternative is pregabalin, which is officially labeled for the treatment of generalized anxiety, and atypical low-potency antipsychotics like quetiapine and olanzapine. Antipsychotics (either typical or atypical) are also prescribed when psychotic symptoms are present. Their side effects include extrapyramidal signs and symptoms, blurred vision, tardive dyskinesia, loss of libido and weight gain.

The therapeutic effect against depression, no matter whether the patient is under monotherapy or combination therapy takes at least two weeks to become evident. There is a number of theories that try to explain it, suggesting that the "down-regulation" of neurotransmitter receptors, or second (post-synaptic intracellular) messenger system alterations or the medium term modulation of neuronal plasticity might be the neurobiological mechanisms underlying the treatment effect. Unfortunately the therapeutic effect of antidepressants does not typically persist more than 36 months after discontinuation and the relapse rate is high and depends on the phase of the disease. It is reported than within the first year, if patients are left without treatment, around 50% of them will relapse if the remitted depressive episode was their first, around 75% if it was the second and maybe up to 90% if it was their third. Thus for those patients with a history of multiple episodes, relapse is almost certain and lifetime treatment necessary (Frank et al. 1990; Kupfer et al. 1992). International guidelines suggest at least 6 months of continuation antidepressant treatment

after the full resolution of the index episode and if the patient is young and the episode was the first or second. For patients with history of episodes treatment should last at least 5 years if not indefinitely.

Regardless of the initial choice of antidepressant, at least 30% of patients will not respond to treatment sufficiently. Clinical impression and recent reports suggest that if there is no response after 3-4 weeks a change of treatment is necessary. Increasing the dosage is one reasonable option since it obviously affects clinical outcome but also increases the adverse effect burden. The maximum dosage recommended by regulatory authorities limits this option. Various alternative treatment strategies have been proposed for these non- or partially responsive depressions, and close work with the patient might produce favorable results. Research is in the way to identify genetic markers predictive of response or useful in the choice of treatment.

The options to treat patients that do not respond adequately to treatment with an antidepressant after 3-4 weeks include the following:

a. Increase the dosage to the highest tolerated or permitted by labeling.

b. Switch to another antidepressant within the same pharmacologic class. Research suggests that failure to tolerate or respond to one medication does not imply failure with other medications.

c. Switch to another agent from a different class of antidepressants gives a 30-50% chance of response (Rush et al. 2006; Thase et al. 2007).

d. Combining two antidepressants from different classes (McGrath et al. 2006)

e. Augmenting the antidepressant with other agents (e.g., lithium, psychostimulants or thyroid hormone)(Bauer et al. 2002a, 2002b)(Nierenberg et al. 2006))

f. Combining the antidepressant with a psychotherapeutic intervention (Thase et al. 2007).

Lithium is well investigated in placebo-controlled trials with positive results and is considered to be the best proven augmentation therapy (Bauer et al. 2002a, 2002b). Aripiprazole is also approved as adjunct therapy on antidepressants for the treatment refractory depression (Hellerstein et al. 2008). Other augmentation options include thyroid hormones (Nierenberg et al. 2006) and psychostimulants (amphetamine, methylphenidate or modafinil) but sometimes they seem to trigger manic or mixed episodes in patients suffering from bipolar disorder and this is particularly problematic to predict when the patient is pseudo-unipolar, that is a manic episode had not been present before. Anticonvulsants are used for patients with alcohol or substance abuse as well as for emotionally labile patients. These patients should not be given stimulants, as they exacerbate mood shifting and put the patient at a risk for abuse. A very frequent practice for refractory patients is the use of combination strategy which involves adding one or more additional antidepressants, usually from different classes. It is expected to use multiple and diverse neurochemical effects to boost treatment; however there is little data to support this practice.

Bipolar Disorder

The treatment of BD is complex and full of caveats for the clinician (Fountoulakis et al. 2005; Fountoulakis, Grunze, Panagiotidis, & Kaprinis, 2007; Fountoulakis, Magiria et al. 2007; Fountoulakis, Vieta et al. 2007). An important problem is that a specific and different treatment needs to be considered separately for manic, hypomanic, mixed and bipolar depression episodes. The first step demands all offending drugs (e.g., stimulants, illicit drugs, caffeine, and sedative-hypnotic agents) should gradually be discontinued, and circadian disruptions and sleep loss minimized.

Today several structured psychoeducational programs exist for patients with bipolar disorder. Hard data concerning the effectiveness of psychosocial interventions in BD are emerging and concern the prophylactic efficacy of cognitive therapy (Ball et al. 2006), family-focused therapy, interpersonal and social rhythm therapy, and cognitive behavior therapy (Miklowitz et al. 2007) and psychoeducation (Colom, Vieta, Martinez-Aran et al. 2003; Colom, Vieta, Reinares et al. 2003; Colom et al. 2004; Colom et al. 2005; Reinares et al. 2004; Scott, Colom, & Vieta, 2006). However, it seems that these modalities are effective only in a selective sample of patients with a rather more benign form of the illness.

The most well known are the following:

a. The behavioral family-management techniques developed by David J. Miklowitz and Michael J. Goldstein which include 21 one-hour sessions after the resolution of the acute phase. They promote family education, communication and problem-solving skills.

b. Monica R. Basco and A. John Rush developed a highly structured three-phase program targeting at educating the patient, teaching cognitive-behavioral skills for coping with symptoms and psychosocial stressors, improving compliance and monitoring the course of the illness.

c. The psychoeducational program developed by Eduar Vieta and Fransesc Colom has similar goals, is highly structured and lasts approximately one year after the resolution of the acute phase. It seems that patients at an earlier stage of the illness have a better prognosis after attending it.

d. Social rhythm interpersonal psychotherapy: This intervention intergrates an interpersonal approach with an effort to stabilize daily activities, especially sleep, eating and working hours.

The biological therapy is the hallmark of bipolar disorder which is considered one of the two major psychotic mental disorders (the other being schizophrenia). Classically the treatment of bipolar illness includes the use of the so-called mood stabilizers (lithium and specific anticonvulsants), antipsychotics and antidepressants.

The first effective medication was lithium salts and for a long time they were considered to be a wonder-like drug both for the acute phase and the prophylaxis. However, it was soon abandoned because of cases of toxicity and was considered unsafe. The problem was that in the beginning it was not possible to monitor plasma levels. Latter lithium's efficacy limitations were evident since half of patients do not respond adequately. Latter, anticonvulsants were proven to be efficacious as well and more recently atypical antipsychotics. The usefulness of antidepressants is somewhat controversial. Several papers with treatment guidelines for BD have been published until today, in an effort to code the way of treatment (Fountoulakis et al. 2005).

Lithium has a well established effectiveness against acute mania (Bowden et al. 1994; Bowden et al. 2005; Keck et al. 2007; Kushner, Khan, Lane, & Olson, 2006) but maybe not against acute depression (Young et al. 2008). The data are far stronger concerning the effectiveness of lithium during the maintainance phase (Bowden et al. 2000; Bowden et al. 2003; Calabrese et al. 2003; Calabrese et al. 2006; Goodwin et al. 2004; Kane et al. 1982). After its discontinuation the likelihood of relapse is very high (50% in the first 5 months and above 80% within the first 18 months). Drawbacks of lithium therapy include its narrow therapeutic index (recommended plasma level 0.8– 1.2 mmol/L), poor tolerability, especially at higher doses, and risk of "rebound mania" on withdrawal (Goodwin, 1994). Common side effects of lithium are tremor, polydipsia, polyuria, and in the long-term, hypothyroidism. However, in spite of these shortcomings, lithium still remains the gold standard of treatment and additionally it might have an antisuicidal effect (Baldessarini et al. 2006; Gonzalez-Pinto et al. 2006).

Of the anticonvulsants, only valproate, carbamazepine and lamotrigine possess data concerning the treatment of bipolar illness. Both valproate and carbamazepine are effective against acute mania (Bowden et al. 1994; Bowden et al. 2006; Pope, McElroy, Keck, & Hudson, 1991; Weisler, Kalali, & Ketter, 2004; Weisler et al. 2005; Weisler et al. 2006) but against acute bipolar depression valproate is effective (Davis, Bartolucci, & Petty, 2005; Ghaemi et al. 2007) while the data concerning carbamazepine are less robust (Ballenger & Post, 1980). The typical dosages for valproic acid are 750-2000 mg daily, with blood concentration 50-120 mg/mL. Rapid oral loading with divalproex using 15 to 20 mg/kg from day 1 of treatment, has been well tolerated and associated with a rapid onset of response. Blood concentrations above 45 mg/mL have also been associated with earlier response. The typical dosages for carbamazepine to treat mania are 600-1800 mg daily and correspond to blood concentrations of 4-12 mg/mL. But for neither agent blood concentrations predict response. An important problem is that after several weeks carbamazepine induces hepatic enzymes thus lowering its levels and requiring an upward dose titration. Lamotrigine seems not to be effective during either the acute manic (unpublished clinical trials) or the acute depressed phase (Goldsmith, Wagstaff, Ibbotson, & Perry, 2003). During the maintenance phase, data are negative for valproate (Bowden et al. 2000), and weak for carbamazepine (Okuma et al. 1981). On the contrary they are strong for lamotrigine but only concerning the prevention of depression (Bowden et al. 2003; Calabrese et al. 2000; Calabrese et al. 2003). The data concerning the other anticonvulsants are either negative (Kushner et al. 2006) or do not exist, although there are open studies and case reports including complicated cases (Oulis et al. 2007). Valproate is reported to possess a relatively high teratogenicity. Other side effects include weight gain and hair loss and maybe the induction of polycystic ovarian syndrome. A potentially life-threatening side-effect of carbamazepine may be the Steven-Johnson syndrome and related dermatologic effects. Lamotrigine has a moderately high incidence of rash, thus titration should be very slow.

All atypical antipsychotics seem to be effective against acute mania (Fountoulakis & Vieta, 2008) but only quetiapine and the olanzapine plus fluoxetine combination are considered to be effective and thus approved against acute bipolar depression (Calabrese et al. 2005; Thase et al. 2006; Tohen, Vieta et al. 2003). Aripiprazole and olanzapine have sufficient data concerning their efficacy during the maintainance phase (and approved) (Keck, Jr. et al. 2007; McQuade, Sanchez, Marcus, & al, 2004; Tohen et al. 2006), although aripiprazole prevented only manic episodes, while data on the efficacy of quetiapine during the maintenance phase have been recently announced and approved (Altamura, Salvadori, Madaro, Santini, &

Mundo, 2003; Altamura et al. 2008). Typical antipsychotics (haloperidol, chlorpromazine, perphenazine) although seem to posses efficacy against acute mania (McIntyre, Brecher, Paulsson, Huizar, & Mullen, 2005; Shopsin, Gershon, Thompson, & Collins, 1975; Smulevich et al. 2005) they also seem to predispose patients to manifest dysphoria or depression (Tohen, Goldberg et al. 2003; Zarate & Tohen, 2004). Adverse effects of antipsychotics include extrapyramidal symptoms and signs, induction of diabetes mellitus and a metabolic syndrome, sedation, hyperprolactinemia and tardive dyskinesia.

Antidepressants should never be used as monotherapy but always together with a mood stabilizer or an atypical antipsychotic, because of the risk to induce the opposite pole, mixed episodes and rapid cycling. Adjunctive studies report that around 14% of bipolar depressed patients under both an antidepressant and a mood stabilizer switch to mania or hypomania (Post et al. 2001; Post et al. 2006). The meta-analysis suggests a higher switch rate for venlafaxine in comparison to SSRIs; however the studies included were randomized trials of adjunctive treatment, maybe including more refractory patients (Leverich et al. 2006). Fluoxetine has a proven efficacy against bipolar depression (Amsterdam et al. 1998; Amsterdam & Shults, 2005a, 2005b; Cohn, Collins, Ashbrook, & Wernicke, 1989) especially in the frame of the combination with olanzapine (E. B. Brown et al. 2006; Tohen, Vieta et al. 2003).

Since in real life the biggest proportion of BD patients do not do well on monotherapy, several combination therapies have been tested and several agents have been tested as an add-on therapeutic option (Fountoulakis & Vieta, 2008).

Other Treatment Modalities

a. Electroconvulsive therapy (ECT) (Daly et al. 2001; Sikdar, Kulhara, Avasthi, & Singh, 1994; Small et al. 1988) could serve as a useful option even in patients who have failed to respond to one or more medications or combined treatment although rigorous data are not available. It can be used both against acute mania and acute depression either unipolar or bipolar. It seems to be effective in both psychotic and nonpsychotic depression, and bilateral ECT is more effective than unilateral, but with more cognitive adverse effects. It is very useful for severely suicidal patients.

b. Transcranial magnetic stimulation (rTMS) (Dolberg, Dannon, Schreiber, & Grunhaus, 2002; Nahas, Kozel, Li, Anderson, & George, 2003; Saba et al. 2004) has shown both some antimanic and antidepressant effects at 20 Hz over the right but not left frontal cortex or at 1 Hz rTMS bifrontally, but the efficacy has not been solidly proven yet.

c. Light therapy is useful for the treatment of mood disorder with seasonal pattern, either as monotherapy or in combination with medication.

Combined Treatment

A significant percentage of mood patients are refractory to any monotherapy. Comorbidity and the successful treatment of the comorbid condition is one of the factors connected to treatment resistance (Sharan & Saxena, 1998). In this frame combination treatment is the

only reasonable strategy, and it is important to embed the antidepressant therapy into a complex therapeutic approach with multiple modalities. However, relatively few studies have investigated its benefits, and in particular, the combination of psychotherapy with antidepressants does not always provide a solidly proven advantage (de Maat et al. 2008; Hegerl et al. 2004).

Psychoeducation and psychotherapy may ameliorate the social problems which appear as a consequence of the mood disorder and might improve compliance with mood-stabilizer agents. A formal approach could be that psychotherapy is used to increase adherence, improve the moral and solve interpersonal and social problems, while medications are used for symptom control. Psychotherapy might be added especially after a partial medication response but it is unclear when this should happen, since the evidence suggests that psychosocial and occupational improvements follow response. Thus, routine use of both treatments initially may not be necessary for psychosocial restoration.

3.0.5 Special Populations/Gender/Cultural Issues

Gender

Studies have shown that nearly all around the world, women have nearly double rates of depression than men although this is not well documented in non-industrialized cultures (Lloyd & Miller, 1997). The National Comorbidity Study reported that 6% of the females vs. 3.8% of males suffered from a current depressive episode and that 21.3% of women vs. 12.7% of men had a lifetime experience of a depressive episode (D. G. Blazer, Kessler, McGonagle, & Swartz, 1994). The rates for bipolar disorder are similar however, suggesting this difference concerns only unipolar depression. A second finding suggests that women with less social support and experiencing social stressors might be at the greatest risk to develop depression. However, there is no significant gender difference concerning the risk of recurrence, thus suggesting that gender is among the risk factors for initiating depressive symptoms but not among those determining the course and outcome. This higher risk for females is present around the age of 20s until the early 30s and that the rates of first onset before (childhood and adolescence) or after that age (middle age, elderly) are similar for both sexes (Nazroo, Edwards, & Brown, 1997; Philibert, Richards, Lynch, & Winokur, 1997).

It seems highly unlikely that there a single, sex-related factor which is responsible for the difference. Endocrine changes and differences were being the target of research without convincing results. The role the female reproductive system might play in mental health is still controversial. The fact that the gender difference is not obvious until puberty, and disappears after menopause, supports the idea that there is something specific connecting the female biology to mood disorders. A more advanced approach suggests that this biology is not a risk factor per se; on the contrary it could be responsible for an increased vulnerability to stressors, thus indirectly leading to depression, especially considering the second fact that women are more likely to experience stressful and even threatening life events and are at a higher risk of early sexual abuse and current spousal abuse (Finkelhor, Hotaling, Lewis, & Smith, 1990; Roesler & McKenzie, 1994). They also might use oral contraceptive use, and often experience mood disorders temporally related to their sexual identity (e.g.,

premenstrual or postpartum-onset mood disorders). Additionally, almost all societies have designated different, unequal roles for women.

On the other hand, since no conclusive data are available so far, it is necessary to consider the possibility that men and women share similar rates of depression, but they express depression in different ways and the resulting different rates is in reality a methodological artifact. In this case, it's reasonable to suggest that different cognitive coping styles between men and women could be responsible for these results and maybe women are more likely to be diagnosed with depression because they seek professional help more often for their depressive symptoms and maybe because they are more sensitive to negative relationships (Phillips & Segal, 1969). It is believed that men might react to emotional distress by trying not to think about it, while women are more likely to ruminate over their problems (Nolen-Hoeksema & Girgus, 1994; Nolen-Hoeksema, Larson, & Grayson, 1999; Nolen-Hoeksema, Stice, Wade, & Bohon, 2007). In this frame, women are more likely to report depressive symptoms due to marital problems than men. This could at least partially be socio-culturally determined, or imposed, since it is reported that the depressed female students who reached out to their friends were met with concerned and nurturing reactions, while in contrasts, the depressed male students who did the same, faced social isolation and often direct rejection, even hostility (Hammen & Peters, 1978; Joiner, Alfano, & Metalsky, 1992). While married, divorced, and separated women were more likely to be depressed than men, widowed men were more likely to be depressed than women and unmarried men and women shared similar rates of depression (Radloff & Rae, 1979).

Another possibility is that in men, but not in women, alcohol abuse could mask an underlying depressive disorder an could account for the difference in the rates. This opinion derives from the observation that alcohol abuse and mood disorders are often inherited in the same family (Triffleman, Marmar, Delucchi, & Ronfeldt, 1995).

Suicide

Today we know that suicide is a complex and multicausal behavior and demands a complex and sophisticated approach. Statistics point to a substantial decline of suicide rates throughout Europe, the US and Canada during the past two decades, and the major reason for that seems to be the better recognition of major depression as well as availability of treatment (Akiskal, Benazzi, Perugi, & Rihmer, 2005; Cipriani, Pretty, Hawton, & Geddes, 2005; Isometsa, Henriksson et al. 1994; Z Rihmer, Belso, & Kiss, 2002; Z. Rihmer & Akiskal, 2006). The understanding and preventing of suicide is one of the most challenging tasks for psychiatry today. It has been confirmed by several psychological autopsy studies that the majority of suicidal victims were suffering from a mood disorder, usually untreated major depression, with frequent comorbidity of anxiety and substance-use disorders (Badawi, Eaton, Myllyluoma, Weimer, & Gallo, 1999; Barraclough, Bunch, Nelson, & Sainsbury, 1974; Henriksson et al. 1993; Monkman, 1987; Rihmer et al. 2002; Rihmer, 2007). Around 60-80% of all suicide victims are suffering from depression while on the other hand, an estimated 15% of patients with severe major depression eventually die from suicide. The rate of attempted to completed suicide, is about 5 to 1 in patients with any mood disorder (Tondo, Isacsson, & Baldessarini, 2003).

Although many risk factors have been identified, most of them are not clinically useful. An important and useful risk factor is the presence of a depressive mixed state (3 or more simultaneously co-occurring hypomanic symptoms in patients with “unipolar depression”). This clinical picture overlaps to a great extent with agitated depression. Depressive mixed state as well as agitation substantially increase the risk of both attempted and committed suicide (Akiskal, Benazzi et al. 2005; Balazs et al. 2006; Isometsa, Henriksson et al. 1994; Rihmer & Akiskal, 2006; Rihmer, 2007). Other risk factors include family history of suicide, higher number of prior depressive episodes, comorbid anxiety, personality disorders and alcohol dependence, as well as sociodemographic and psycho-social factors such as younger age, being divorced or widowed, and experiencing adverse life-situations which are associated with increased suicidal ideation and higher prevalence of attempts (Balazs et al. 2006; Bernal et al. 2006; Henriksson et al. 1993; Rihmer et al. 2002; Z. Rihmer & Akiskal, 2006; Z. Rihmer, 2007). Although biological research has so far identified several biological correlates of suicide today there is no biological marker found yet to distinguish explicitly between suicidal and non suicidal depressives (Nordstrom et al. 1994; Samuelsson, Jokinen, Nordstrom, & Nordstrom, 2006).

An impressive fact is that in spite of frequent medical contact before committing suicide, only a small minority of victims had received appropriate treatment. This is particularly a problem in primary care, where most patients seek help (Henriksson et al. 1993; Isometsa, Aro, Henriksson, Heikkinen, & Lonnqvist, 1994; Luoma, Martin, & Pearson, 2002; Z. Rihmer, Barsi, Arato, & Demeter, 1990; Rihmer et al. 2002). Thus not only early identification of suicidal behavior is possible but also early intervention is possible and could make a difference. The patient should be put on a plan of regular psychiatric visits on an interval ranging from once to twice weekly. Latter visits could be planned on a month interval or even less frequently. The main factors determining frequency include the clinical picture, social and family support, history of adherence, insight into the illness and the risk and medication adverse effects. The therapist should have in mind that antidepressive agents are the only formally approved treatment for major depression (Akiskal, Benazzi et al. 2005; Z. Rihmer & Akiskal, 2006; Yerevanian, Koek, Feusner, Hwang, & Mintz, 2004) and there are no data supporting the effectiveness of any other approach (Fountoulakis, Gonda, Siamouli, & Rihmer, 2008). Also a marked anti-suicidal effect has been also reported with long-term lithium therapy in bipolar (manic-depressive) patients (J. Angst, Angst, Gerber-Werder, & Gamma, 2005; Cipriani et al. 2005; Rihmer & Akiskal, 2006). Recently, the U.S. Food and Drug Administration issued a warning concerning the use of antidepressants in children and adolescents and possibly in all age groups because of possible induction of suicidality (thinking and behavior but not completed suicide) by antidepressants in juvenile depressives (FDA, 2009). A similar warning is in place now concerning anticonvulsants. However, the impact of this warning might be robustly negative.

The warnings are based on data from RCTs but there is doubt whether the design of these studies permit these conclusions. A recent study reports that after the warning, (between 2003 and 2005) the SSRIs prescriptions for children and adolescents in the US and the Netherlands decreased by about 22% but simultaneously there was a 49% youth suicide rate increase in the Netherlands (between 2003 and 2005) and a 14% in the US (between 2003 and 2004) (Gibbons et al. 2007). It is highly possible the "natural" population of mood disorders patients does not respond to treatment this way. On the contrary it seems that proper and "aggressive" treatment of mental disorders and especially of major depression aiming at achieving full remission should always be the target and determines to a large extent

whether suicidal behavior is expressed or not (Angst et al. 2005; Moller, 2006; Sondergard, Lopez, Andersen, & Kessing, 2007; Tiihonen et al. 2006). However, a caveat is that the most dangerous period for suicide in a patient is immediately after treatment has commenced, as antidepressants may reduce the symptoms of depression such as psychomotor retardation or lack of motivation before mood starts to improve. Although this appears to be a paradox, studies indicate the suicidal ideation is a relatively common component of the initial phases of improvement even with psychotherapy (Moller, 1992).

Substance Use Comorbidity

Substance use and abuse is an old problem which recently gained significant importance. A large variety of different substances could be related with use or abuse and consequently with substance-induced mood disorders (Schuckit et al. 1997; Winokur et al. 1998). They include various medications (e.g., anesthetics, anticholinergics, antidepressants, anticonvulsants, antibiotics, antihypertensives, corticosteroids, antiparkinson agents, chemotherapeutic agents, nonsteroidal anti-inflammatory drugs, and disulfiram), toxic agents (heavy metals, industrial solvents, household cleaning agents), or substances used routinely for recreational purposes (e.g., caffeine, nicotine). Almost all the substances are preferred because of their subjective effects which concern mainly the mood. Others are used for their calming or "therapeutic-like" effect (as self-treatment, e.g., alcohol, sedatives) while others for their stimulating, euphoric and augmenting effect (e.g., stimulants).

Substance use and abuse could happen in the frame of a pre-existing mood disorder or the use itself can be the cause of the disorder (because of the direct physiological effects, toxicosis, withdrawal or dependence). When the mood disorder is primary and pre-exists, substance use complicates both the clinical manifestations and the treatment, and might lead to poor prognosis. This is especially often during teenage and early adult years, and relates mainly to cyclothymia and probably represents attempts of self-medication for the mood liability. During the withdrawal period many substances including alcohol, opioids, and sedatives might induce persistent mood disturbance, insomnia and cognitive disorder leading to relapse of the abuse. These symptoms need to be distinguished from those of primary mental disorders, and this is often very difficult. The critical factor is the clinician's judgment that the mood disorder is caused by the substance or not. A double diagnosis is usually the only reasonable solution. However, the "self-medication" scenario with mood disorder being primary, or even the double diagnosis are unfortunately not the diagnostic priority of many therapists (especially in therapeutic communities) and consequently, the missing of the diagnosis of mood disorder deprives the patient from proper and effective treatment.

Alcohol use and abuse is very frequent especially for mood and anxiety patients. On the other hand, heavy alcohol consumption over a period of days results in a depressive state, which even when it is severe, it largely improves within days to weeks of abstinence. After several weeks, most alcoholic patients manifest residual low mood or mood swings resembling a cyclothymic or dysthymic disorder but they also tend to diminish and disappear with time. The presence of the dysthymic symptoms usually indicates the normal course of a withdrawal syndrome and not an independent mood disorder. Nicotine use and abuse is also very frequent usually in the form of cigarette smoking and withdrawal is manifested by

changes in mood, anxiety and weight gain (average is 2 to 3 kg) which can persist even for months.

Amphetamine, cocaine, opioid, hallucinogen or inhalant - induced mood disorder can occur during intoxication or withdrawal. In general, for all this substances, intoxication is associated with manic or mixed mood features, whereas withdrawal is associated with depressive mood features. An induced mood disorder by any of them usually remits within a week or two (several weeks for opioids), except from panic episodes that develop during cocaine use which could persist for many months following cessation (Krystal, Price, Opsahl, Ricaurte, & Heninger, 1992; Weddington et al. 1990). An important outcome is suicide which is not an uncommon complication.

Pediatric

Although the core features of mood disorders are essentially the same across the life span, traditionally children and the elderly are considered somewhat separately because of the special features their phase of life includes and the way these features might influence the overall manifestation of mental disorders and their treatment. Additionally, an early age of onset of any disorder puts forward the question whether this determines a more severe and chronic disease and also poor response to treatment.

It seems that the developmental phase might influence the expression of certain mood symptoms and that's why e.g., pervasive anhedonia or significant psychomotor retardation are rare among depressive children and auditory hallucinations and somatic complaints are seen more often in prepubertal children.

The incidence of mood disorders among children and adolescents is reported to increase during the last few decades. These reports are rather consistence and they also suggest there is a decrease of the age of onset of mood disorders. The general picture suggests that the prevalence of depression is around 0.3% for pre-school children, 0.4–3% for school aged children and 0.4–6.4% for adolescents; the prevalence of bipolar disorder is 0.2–0.4% in children and 1% in adolescents. Research suggests that 40-70% of children and adolescents with a mood disorder have also at least one comorbid psychiatric disorder. The risk factors as well as the etiopathogenesis for this age group are uncertain.

Concerning suicide and related behavior, the attempted suicide is 1% in children and 1.7–5.9% in adolescents, while the completed suicide rate ranges from nearly zero in children below the age of 10, to a peak of above 18/100,000 in boys 15-19 years old. The data suggest that among 15-19 year-olds, the suicide rates have quadrupled over the last four decades, and the reason for this is not known. Unfortunately, suicide is currently the fourth leading cause of death in children aged 10-15 years and the third leading cause of death among adolescents and young adults aged 15-25 years. The suicidal method is the most significant factor which determines whether the attempt will result in death. The great majority of attempts among children and adolescents have little lethal potential partially because of restricted access to lethal material and inadequate cognitive potential to plan a successful attempt. What is unique in this age group is suicide imitation and contagion. This means that the suicidal behavior increases in adolescents following exposure to well-publicized news stories of suicide or a film involving a teen suicide, but this seems to concern vulnerable

individuals and not the age group as a whole (Brent et al. 1993; Cheng, Hawton, Lee, & Chen, 2007; Gould & Shaffer, 1986).

The etiopathogenesis of mood disorders in children and adolescents is not well understood. It is an age group which combines developmental vulnerability and high potency for neuroplastisity and compensation for any insults. It is generally believed that genetic factors play a significant role; however there are vague data in support of this and no clear conclusions can be made. Non-shared environmental factors might also play an important role (Pike & Plomin, 1996). At the cognitive level, the theoretical approach suggests the presence of cognitive distortions similar to those seen in adults but again data are inconsistent and scarce.

Traditionally there has been significant interest on the family interactions and their relationship to the development of depression, but the conditions are usually complicated and difficult to interpret. The most difficult problem is that when the family environment is problematic, then, there is a high probability of a genetic vulnerability in the family and sometimes in both parents. However, this does not exclude the possibility the environment to induce a kind of emotional vulnerability in the child by shaping the early experiences. Depressed parents may model negative cognitive styles and poor self-esteem, leading to a deficit of social problem-solving skills and in coping with stressful life events; marital conflict and lack of an adequate family support system especially when a mental illness of the parent(s) of an early onset, is recurrent, and disrupts parental functioning puts the child at a high risk for any mental disorder but especially for a mood disorder. In this frame, it is understandable why family conflict is the most frequent event adolescents report they experienced, before they manifest suicidal behavior. There are several studies suggesting that depressed children and adolescents might experience more stressful life events like interpersonal losses, problems in relationships, parental divorce, bereavement, physical abuse and suicide in the environment (Beautrais, Joyce, & Mulder, 1997; Gould, Shaffer, Fisher, & Garfinkel, 1998; Kaplan, Pelcovitz, Salzinger, Mandel, & Weiner, 1997; Williamson, Birmaher, Anderson, al-Shabbout, & Ryan, 1995).

The conclusion concerning the etiopathogenesis of mood disorders in children and adolescence is that genetics clearly plays at least a moderate role while both shared and non-shared environmental influences appear to be also important.

Clinically depression in this age group presents with the same core features manifested in adults. Some minor differences suggest the presence of irritable rather than depressed mood and failure to attain expected weight gain instead of weight loss. Among pre-school children often lack of smiling, apathy towards play, lack of involvement in all activities, physical complaints, and physical aggression while among school-aged children, deteriorating school performance, increased irritability, fighting, or argumentativeness and avoidance of peers may signal depression. Exacerbation of anxiety symptoms and school refusal are not uncommon among children who are depressed.

Switching from unipolar depression to bipolar disorder is significantly higher in children than it is in adults, and it reaches 32% within a 5 year period. Also, it is reported that in children, mania might present with a chronic instead of an episodic pattern, with mixed and rapid cycling features instead of classic manifestations and high comorbid mental disorders. These suggest that childhood-onset bipolar disorder is a more severe form of the illness, and relatively treatment resistant. The main disorders that should be differentially diagnosed are

attention-deficit/hyperactivity disorder and disruptive behavior disorders (Geller & Luby, 1997).

The psychological treatment of children and adolescents with mood disorders are similar to those for adults. On the contrary there is a significant controversy concerning pharmacotherapy. Double-blind studies are missing and it seems that these age groups are particularly vulnerable for the induction of suicidality by antidepressants. Flouxetine, quetiapine and lithium are the better studied agents in terms of efficacy in these age groups (Andrade, Bhakta, & Singh, 2006; Azorin & Findling, 2007; Barzman, DelBello, Adler, Stanford, & Strakowski, 2006; Chang, 2008; DelBello et al. 2006; DelBello, Adler, Whitsel, Stanford, & Strakowski, 2007; Dudley, Hadzi-Pavlovic, Andrews, & Perich, 2008; Jensen, Buitelaar, Pandina, Binder, & Haas, 2007; Marchand, Wirth, & Simon, 2004; Tsapakis, Soldani, Tondo, & Baldessarini, 2008; Usala, Clavenna, Zuddas, & Bonati, 2008). ECT and TMS might be reasonable alternatives if initial therapeutic attempts fail (Morales, Henry, Nobler, Wassermann, & Lisanby, 2005).

Geriatric

A world wide trend is the increase in both the absolute numbers and percentage in the total population of the elderly. This of course leads to an increase in the numbers of geriatric psychiatric patients and a shift of the focus of health care services. At the same time, geriatric mental patients present with multiple challenges both at the diagnostic as well as the therapeutic level.

The prevalence of major depression is estimated to be 2% in the general population over 65 years of age (Blazer, Burchetti, Service, & al, 1991; Reynolds, 1992; Vaillant, Orav, Meyer, McCullough Vaillant, & Roston, 1996), with up to 15% having some kind of other mood disorder (Branconnierm et al. 1983) and 25-40% of patients in the general hospital setting having a sub-threshold depression (Rapp, Parisi, & Walsh, 1988). In residential homes, the accepted value for patients with MDD is approximately 12%, with an additional 30% manifesting a milder form of depressive-like symptomatology (Foster, Cataldo, & Boksay, 1991; Katz, Lesher, Kleban, Jethanandani, & Parmelee, 1989; Katz & Parmelee, 1994; NIH, 1992; Parmelee, Kleban, Lawton, & Katz, 1991; Weyerer, Hafner, Mann, Ames, & Graham, 1995).

The recognition of geriatric mood patients (with a late onset mood disorder) is poor and less than 50% of hospitalised patients with depression in general medical practice are referred to a psychiatrist, and less than 20% receive adequate treatment (Shah & De, 1998). The same time, geriatric patients with depression have up to 1.5-3 times higher morbidity (Parmelee, Kalz, & Lawton, 1992), with the lifetime risk of suicide being as high as 15%; almost 10% of them die annually (Murphy, 1994). The ratio of males to females with MDD remains stable across the age spectrum (PW Burvill, Hall, Stampfer, & Emmerson, 1989).

Late onset mood patients are less likely to have a positive family history for mood disorders compared to younger patients (Hopkinson, 1964; Mendlewicz, 1976) and are more likely to manifest structural changes of the CNS (Burvill et al. 1989; Jacoby & Levy, 1980; Rabins, Pearlson, Aylward, Kumar, & Dowell, 1991). Neuroimaging studies have reported a variety of morphological disturbances, which clearly differentiate late-life depression from

depression of younger ages (Greenwald et al. 1996; Jakoby, Lewy, & Bird, 1980, 1981; Rabins et al. 1991; Sackheim, Prohonik, Moeller, & al., 1993; Steffens & Krishnan, 1998; Uradhyaya, Abou-Saleh, Wilson, Grime, & Critchley, 1990), clearly suggesting an association to an increased severity of subcortical vascular disease and greater impairment of cognitive performance (Salloway et al. 1996). More, major depression is more common and more severe in patients with vascular dementia (Ballard, Bannister, Solis, Oyebode, & Wilcock, 1996).

Various studies of depression in the elderly reported that mood is more often irritable than depressive (Monfort, 1995), and also several symptoms like loss of weight, feelings of guilt, suicidal ideation, melancholic features, hypochondriasis as well as associated symptoms of psychosis could be more frequent (Brown, Sweeney, Loutsch, Kocsis, & Frances, 1984; Lader, 1982; Lyness, Conwell, & Nelson, 1992; Musetti, Perugi, Soriani, Rossi, & Cassano, 1989; Nelson, Conwell, Kim, & Mazure, 1989). However, these findings vary across studies. Many of these patients manifest a type of behavior that can be characterized as "passive-aggressive" or "self-aggressive." They refuse to get up from bed, eat, wash themselves, or talk. Also, they often hide important information concerning severe somatic disease and in this way they let it go untreated.

Somatic symptoms are difficult to assess and, as a general rule, physicians should avoid assigning this symptomatology to an underlying mental disorder. It is highly likely the patient indeed suffers from a true "somatic" disorder even in cases the physician is unable to diagnose it (APA, 1994). On the other hand, it is clear that elderly depressives manifest more somatoform symptomatology, in comparison to younger depressives. In this frame, the concept of Masked Depression (Modai, Bleich, & Gygielman, 1982) used to be popular in the past, but today it is not accepted by either classification system although it is accepted that the onset of health concerns in old age is more likely to be either realistic or to reflect a mood disorder (APA, 1994). Percentages of comorbidity between depression and physical illness vary from 6% to 45% (Kitchell, Barnes, Veith, & al. 1982; Kok, Heeren, Hooijer, & al., 1995). The large discrepancy reflects the difficulty in the application of operationalized criteria for the diagnosis of depression in patients with general health problems. Greater overall severity of medical illness, cognitive impairment, physical disability and symptoms of pain or other somatic complaints seem to be a more important predictor of depression than specific medical diagnoses (Williamson & Schulz, 1992).

About 38-58% (Alexopoulos, 1991) of the elderly suffering from major depression also fulfill criteria for an anxiety disorder while many authors have suggested that the presence of anxiety in the elderly should be considered as a sign of depression, even in cases, which lack true depressive symptomatology (Collins, Katona, & Orrell, 1994).

In elderly individuals there is an increased possibility of the co-existence of depression and dementia, or some other type of "organic" decline of cognitive disorder. The syndrome of "pseudodementia" has also been described (Kiloh, 1961). This term refers to the manifestation of dementia symptomatology, which in fact is due to depression and disappears after antidepressant therapy. It is also described the emergence of late onset bipolarity in the frame of an ongoing dementing pathology (Akiskal & Pinto, 1999; Akiskal & Benazzi, 2005; Ng et al. 2007)

Suicide constitutes an important health problem for the elderly. Elderly men are at a higher risk for completing suicide than elderly women. The co-existence of a serious somatic disease,

like renal failure or cancer, represents a major risk factor for a well-planned suicide attempt (Heikkinen & Lonnqvist, 1995). Other risk factors include loneliness and social isolation, usually as a consequence of bereavement. The failure to follow medical advice in serious general medical conditions could be considered to be a form of "passive suicide." On the other hand, "rational" suicide plans are not common even in severely ill patients. There is a possibility of acute-onset suicidal plans (after an acute incidence concerning general health e.g., stroke or heart attack) (Kishi, Robinson, & Kosier, 1996).

The pharmacotherapy of late-onset mood disorder includes the cautious use of antidepressants including amitriptyline, imipramine, nortriptyline and all the SSRIs which are most widely prescribed antidepressants among the geriatric population, because of their favorable side-effect profile, relative safety in overdose, ease of use and smaller dosage adjustment makes them first-line choices. Also venlafaxine, mirtazapine, and bupropion could be useful.

For bipolar cases, lithium and anticonvulsants are useful although they are not well studied in elderly patients (Fountoulakis et al. 2003). It is mostly used in cases of refractory depression for the augmentation of antidepressant therapy. Antipsychotics, especially second generation ones could be used although there is a warning for a higher mortality because of their use in the elderly. ECT is another option with many studies reporting better outcomes in older than in younger patients. However, by far the most troubling side effect of ECT, especially in the elderly, is cognitive impairment.

Psychotherapy is also an option (Gerson, Belin, Kaufman, Mintz, & Jarvik, 1999; Gum & Arean, 2004). The presence and severity of medical illnesses, physical disability, cognitive impairment and psychomotor retardation make psychotherapeutic intervention difficult and affect its efficacy and success. The form of psychotherapy should be adjusted to the patient's personality, behavior patterns as well as his/her cultural and educational level. Behavioral therapy, cognitive-behavioral therapy and problem-solving therapy have been extensively studied for their effectiveness in the treatment of depression in elderly. Fewer studies have been carried out for the efficacy of interpersonal psychotherapy. Non-standardized psychotherapies such as, psychodynamic psychotherapy and reminiscence therapy, are also proposed as appropriate treatments for geriatric depression.

The combination of pharmacological and psychological treatments is associated with higher improvement rates than pharmacotherapy alone and considered more effective than either treatment alone in preventing recurrence of depression (Bartels et al. 2002). In long-term therapies, the addition of psychotherapy promotes adherence to treatment (Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004).

Eventually however, most studies support the opinion that geriatric depression carries a poorer prognosis than depression in younger patients. However, many authors attribute this, to factors like failure to make an early diagnosis and improper or insufficient treatment. For patients with geriatric depression, the prognosis is more dependent on physical handicap or illness and lack of social support, however further research on this issue is needed. Thus, the effective prevention of late-life depression requires attention to maintaining the community infrastructure and support.

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4 Somatoform Disorders

Introduction

The somatoform disorders have in common the "repeated presentation of physical symptoms, together with persistent requests for medical investigations, in spite of repeated negative findings and reassurances by doctors that the symptoms have no physical basis" (World Health Organization, 1992). Psychiatrists worldwide use either the ICD-10 or DSM-IV systems of classification when diagnosing mental illness. For most conditions there is little difference between the two systems, but for the somatoform disorders the conditions included differ slightly – see Table 1 for details.

Table 1: Comparison of Somatoform Disorders: ICD-10 vs. DSM-IV

ICD-10Somatoform Disorders (F45)	**DSM-IVSomatoform Disorders (300)**
Somatization disorder	Somatization disorder
Undifferentiated somatoform disorder	Undifferentiated somatoform disorder
Hypochondriacal disorders (includes Body dysmorphic disorder)	Hypochondriasis
	Body dysmorphic disorder
Somatoform autonomic dysfunction	
Persistent somatoform pain disorder	Pain disorder
Other somatoform disorders	
Somatoform disorder, unspecified	Somatoform disorder, not otherwise specified

For the purposes of this chapter we take an inclusive view of disorders loosely grouped under the somatoform label and cover the following conditions: • Somatization Disorder • Hypochondriacal Disorder • Somatoform Pain Disorder and Chronic Pain • Conversion (Dissociative Motor) Disorder • Body Dysmorphic Disorder • Functional Somatic Syndromes (e.g., chronic fatigue syndrome/myalgic encephalomyelitis, fibromyalgia, chronic pelvic pain, multiple chemical sensitivity).

The Somatoform Disorders are important to recognise because they are relatively common, costly and almost invariably present to doctors other than psychiatrists. In addition, many doctors find patients with these disorders difficult to understand and treat. The feature that all of these illnesses have in common is the patient's experience of medically unexplained symptoms, which refers to physical (or somatic) symptoms that are disproportionate to identifiable physical disease.

Terminology

The terminology is confusing in this area, as many terms are used interchangeably. For example, although we often use the term medically unexplained symptoms in this chapter you may also encounter terms such as "somatization," "functional symptoms" or "hysterical symptoms" seemingly referring to the same thing. It is possible for one patient to fulfil diagnostic criteria for several somatoform disorders at one time (e.g., somatoform pain disorder and dissociative disorder) which has led to criticism of current diagnostic systems, and it is likely that future versions of ICD/DSM will change how such disorders are defined (Kroenke, Sharpe et al. 2007).

To make matters worse, psychiatrists often use different diagnostic terminology to that used by their medical colleagues; these differences can hamper doctors' ability to come to a shared understanding of a patient's problems. Take, for example, a woman who suffers from a wide number and range of symptoms for which no adequate pathological cause has been found. These symptoms have been present for many years, have resulted in marked disability and, despite a long history of consultations with many different doctors, there has been no improvement. The woman's medically unexplained symptoms include fatigue, dizziness, headache, subjective limb weakness and painful joints. A psychiatrist makes a diagnosis of "somatization disorder," whilst a rheumatologist diagnoses "fibromyalgia" and a neurologist "chronic fatigue syndrome/myalgic encephalomyelitis." The patient herself rejects all of these diagnoses and prefers to think of herself as having "multiple chemical sensitivity." In the field of the somatoform disorders, the labels often say more about the specialty of the person applying them than any underlying pathology. The lesson to learn here is that these diagnostic labels are descriptive, often overlapping and seldom uncontentious.

Phenomenology

Clinical Symptoms and Classification

All somatoform disorders are highly co-morbid (i.e., co-exist) with each other and with anxiety and depression. Therefore screening for anxiety and depression, which are treatable, should be undertaken in any patient presenting with a medically unexplained syndrome. In the following section we go through the somatoform disorders in turn and highlight their diagnostic features. The diagnostic descriptions are based on ICD-10 criteria where possible. We emphasise from the outset that the classification of the so called somatoform disorders is a mess, which we hope (perhaps optimistically) will be improved in the current revisions of both ICD and DSM:

i) Somatization Disorder The patient has a history of multiple and recurrent medically unexplained symptoms (>6 symptoms) starting in early adult life and lasting for at least 2 years. The symptoms cause distress and impairment and lead to repetitive consultations with medical personnel that are typically unhelpful. There is usually a history of unnecessary or unhelpful investigations or procedures and the patient may have a high level of disability. These patients commonly present to many different specialists and are high users of health care resources.

ii) Hypochondriacal Disorder The patient is persistently preoccupied (for > 6 months) and distressed with the possibility of having one or more serious illnesses. This health anxiety persists despite repeated medical reassurance that they do not suffer from the feared illness(es). There is overlap with obsessive-compulsive disorder.

iii) Somatoform Pain Disorder and Chronic Pain The patient has persistent (> 6 months), severe and distressing pain that is not fully explained by a physical disorder and they are pre-occupied by their pain symptoms. Chronic pain is also a common symptom in somatization disorder.

iv) Conversion (or Dissociative Motor) Disorder The patient has motor or sensory symptoms (e.g., seizures, paralysis, loss of speech, blindness) for which there is inadequate physical explanation. There is usually considerable disability associated with the symptoms. The patient should not be intentionally feigning the symptoms. This disorder was of great interest to early neurologists and psychiatrists including Charcot, Janet and Freud, when it was known as hysteria. The term conversion disorder originally implied that psychological symptoms (or conflicts) were converted to motor symptoms, although this rather simplistic view is now outdated (Halligan, Bass et al. 2000). Nevertheless, in practice clinicians treating these patients expect to be able to determine psychological or emotional factors that are contributing to the patient's presentation.

v) Body Dysmorphic Disorder The patient has a persistent preoccupation that a part of the body is diseased or deformed, when to an objective observer it is not. The patient will often pursue surgical or other cosmetic treatments in order to correct the perceived deformity and therefore commonly present to dermatologists or cosmetic surgeons. In ICD-10 this disorder is classified within hypochondriacal disorder, but DSM-IV prefers to keep it as a distinct disorder. Many psychiatric researchers believe that body dysmorphic disorder would actually be better classified as an anxiety disorder because there is often considerable overlap with obsessive compulsive disorder.

iv) Functional Somatic Syndromes The functional somatic syndromes refer to a number of related syndromes that have been characterised by the reporting of somatic symptoms and resultant disability rather than on the evidence of underlying conventional disease processes. Many such syndromes have been described. Some of these - such as irritable bowel syndrome - are well recognised within mainstream medicine but others - such as sick building syndrome - are not. All however share the feature of a disconnection between subjective symptomatology and objective biomedical pathology. Most medical specialities have at least one functional somatic syndrome – see Table 2 for examples.

Table 2: Functional somatic syndromes by medical speciality

Medical Specialty	**Functional Somatic Syndrome**
Gastroenterology	Irritable bowel syndrome
Rheumatology	FibromyalgiaRepetitive strain injury
Cardiology	Non cardiac chest pain
Infectious Disease	Chronic fatigue syndrome/myalgic encephalomyelitis(sero-negative) Lyme Disease
Respiratory Medicine	Hyperventilation syndrome
Dentistry	Atypical facial painTemporomandibular joint dysfunction

Medical Specialty	Functional Somatic Syndrome
Ear Nose & Throat	Globus syndrome
Neurology	Tension-type headache
Non allied syndromes	Gulf War syndromeChronic whiplashSick building syndromeCandidiasis hypersensitivityMultiple chemical hypersensitivity

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), irritable bowel syndrome and fibromyalgia, have been more extensively researched than most other functional somatic syndromes, which has led to specific pathophysiological mechanisms being advanced for each and the development of widely accepted diagnostic criteria. Nevertheless, as yet no specific explanation is compelling and it remains the case that the similarities between the different syndromes are sufficiently striking for there to be a compelling case for considering them together (Barsky and Borus 1999; Wessely, Nimnuan et al. 1999).

Commonly used diagnostic criteria for the three most well known functional somatic syndromes are outlined below:

Chronic fatigue syndrome/Myalgic encephalomyelitis (CFS/ME) (Fukuda, Straus et al. 1994)

- 6 months disabling fatigue
- Substantially reduced activity
- At least 4 of these symptoms:
  - Impaired memory or concentration
  - Sore throat
  - Tender glands
  - Aching/stiff muscles
  - Multiple joint pains
  - New Headaches
  - Unrefreshing sleep
  - Post-exertional fatigue

Irritable bowel syndrome (Rome Foundation, 2006)

- Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with ≥2 of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in the form (appearance) or the stool

Fibromyalgia (Wolfe, Smythe et al. 1990)

- Widespread pain in combination with...
- Tenderness at ≥11 of 18 specific tender point sites

Epidemiology

Somatic symptoms are common and are the main reason why people seek medical care. Around a third of somatic symptoms that are seen in primary care can be classified as medically unexplained (Kroenke, 2003), whilst the proportion is at least as high in secondary care clinics (Nimnuan, Hotopf et al. 2001; Reid, Wessely et al. 2001; Carson, Best et al.

2003). The prevalence (frequency) of the specific somatoform disorders varies depending on the setting and the diagnostic criteria used. For example the population prevalence of strictly defined somatisation disorder is around 0.5%, but rises to as much as 16.6% when abridged criteria are used (Creed and Barsky, 2004). Likewise the population prevalence of hypochondriacal disorder has been estimated at between 0.02% and 7.7%, with abridged criteria suggesting a prevalence as high as 10.7% (Creed and Barsky, 2004). Body dysmorphic disorder is believed to be present in approximately 1-2% of the general population (Mackley, 2005). Fewer studies have looked at the epidemiology of somatoform pain or conversion disorders, and once again differing diagnostic criteria and populations lead to difficulties in interpretation. Prevalence estimates for the commonest functional somatic syndromes are shown in Table 3. Most epidemiological research in the functional somatic syndromes has focussed on the prevalence of CFS/ME, fibromyalgia and irritable bowel syndrome - probably because operational criteria exist for these disorders.

Table 3: Prevalence figures for a sample of functional somatic syndromes

Functional Somatic Syndrome	Estimated population prevalence
Chronic fatigue syndrome	0.007 – 0.56% (Ranjith, 2005)
Irritable bowel syndrome	3 – 20% (Brandt, Bjorkman et al. 2002)
Fibromyalgia	0.5 – 5% (Neumann and Buskila, 2003)
Non cardiac chest pain	25% (Fass and Dickman, 2006)
Chronic pelvic pain	15% women (Zondervan and Barlow, 2000)
Tension-type headache	38% (Jensen and Stovner, 2008)

Most research shows that women suffer from somatoform disorders more frequently than men, with the probable exceptions of hypochondriacal disorder and body dysmorphic disorder. A low level of education is also a risk factor. Other aetiological factors are reviewed below under "Assessment."

Assessment

Allow adequate time Adequate time should be allowed for assessment of patients with medically unexplained symptoms. Although this can be difficult in the setting of a busy primary care clinic or medical outpatients, time spent engaging the patient and gaining a full history will pay dividends later. Patients with severe and enduring medically unexplained symptoms will often have had negative experiences of medical care in the past (Reid, Ewan et al. 1991) (Deale and Wessely, 2001) and it is important that the patient feels believed whenever they are seen by a new health care professional. Therefore good communication skills are important.

Start with the symptoms A good place to start is by taking an exhaustive and full history of all current symptoms. This is not solely for (or even for the purposes of) making a diagnosis, but to demonstrate to the patient that they are being taken seriously and it gives an indication of the way that the patient relates to their symptoms. Duration, severity, exacerbating and relieving factors should be explored for the main symptoms. One of the most neglected questions is to ask the patient what their concerns are about their symptoms (e.g., are they worried that they have cancer?). As a general rule, the more symptoms someone has, the more likely they are to be medically unexplained. It is useful to understand how impaired someone is by their symptoms on a day to day basis and how their

illness impacts on their life. When the opportunity arises, psychosocial difficulties should be explored; the easiest way to do this is to use the patient's own terminology to ask about an area more fully (e.g., if a patient mentions they are "stressed," you can use this word to ask them what is difficult for them in their life). This can help you understand the patient's illness behaviour better i.e., how does the patient behave when they are symptomatic? Do their symptoms enable them to avoid situations that are stressful? Understanding what the patient attributes their symptoms to can help you explain how unhelpful patterns may have emerged (e.g., a person with CFS/ME who believes their symptoms are due to work stress will behave and manage their symptoms very differently from someone who attributes identical symptoms to a persistent viral infection.

Review previous notes It is preferable to have read previous notes and investigations before meeting the patient, although this is not always possible. It is essential to review old notes before ordering more investigations, as repeating old investigations for previously investigated symptoms can lead to iatrogenic harm (Page and Wessely, 2003). A notes review can add valuable information on previous symptoms or past diagnoses (including somatoform disorders). It also offers an important insight into how the patient interacts with doctors and other doctors' opinions of the patients' problems.

Rule out anxiety and depression Patients with anxiety or depression commonly present with physical rather than emotional symptoms. Both anxiety and depression are often experienced physically (e.g., anxiety can present with difficulty swallowing, stomach unease, sweaty palms; depression can present with weight loss, poor appetite, low energy). However, most patients will talk about the emotional symptoms of anxiety and depression if the topic is approached sensitively. Because the terms "anxiety" and "depression" are not universally understood, it is useful to have some probing questions you can use that are suitable for the culture in which you are working. Some examples of questions that are suitable for use in the Western setting are shown in Table 4.

Table 4: Example probe questions when screening for anxiety or depression

Anxiety	**Depression**
Do you often feel tense?Do you find yourself worrying a lot?Do you ever feel panicky?Is it difficult for you to relax?Do you feel keyed-up most of the time?	Do you feel low or down very much?Do you still enjoy things as much as you used to?Do you feel slowed down?Are you often aware of feeling sad or miserable?Do you feel hopeful about the future?

Communication For patients with medically unexplained symptoms the first consultation with a new doctor is important. As mentioned above, these patients have often had negative experiences of medical consultations in the past, so an empathic manner and sensitively taken history can be therapeutic in itself. It is never a good idea to imply that you don't find a patient's symptoms credible or that there is "nothing wrong" because investigations have been negative. The patient's symptoms are real and often uncomfortable, even if their patho-physiology is unclear. Many doctors dislike it if a patient expresses negative sentiments about their colleagues or other services. For the most part it is not necessary to enter into an argument with the patient about the rights and wrongs of their previous

medical encounters, instead respond to the emotional content of what the patient is saying rather than the specifics (e.g., "that must have made you feel very angry").

Pathogenesis

One issue around all medically unexplained syndromes is when do they become medically explained? Everyone remembers genuine breakthroughs in our understanding of health and disease; one such example being the discovery that General Paresis of the Insane (GPI) (sufferers of which could be found in all the asylums of Europe at the end of the 19th century) was a manifestation of neurosyphilis. When, a generation later, penicillin was found to kill the causative agent, GPI largely disappeared. In our own time, generations of doctors had been taught that peptic ulcer was due to excessive acid secretion, itself the result of stress: that is until Helicobacter Pylori was identified.

But we should also pause for thought. First, the traffic is not all one way. For every previously viewed unexplained or psychiatric illness whose "medical" cause is identified, there is an equal and opposite traffic, as previously viewed medical entities such as visceral proptosis, autointoxication, floating kidneys, chronic appendicitis and so on and so on make the opposite journey. Second, many of the mechanisms that we highlight in this contribution do not cease to be relevant once a causative organism or factor is identified – far from it. The same issues remain relevant, for example psychosocially informed treatments (e.g., Cognitive Behavioural Therapy) do not lose their effectiveness, which is not surprising given that they are of proven efficacy in improving outcome in conditions as diverse as cancer, rheumatoid arthritis, multiple sclerosis, HIV related illness and so on.

Somatoform disorders are best thought of as multi-factorial in origin. It is rare than one mechanism (be it emotional or physical) is responsible for a patient's symptoms. When thinking about why a patient is suffering from medically unexplained symptoms, the traditional psychiatric formulation is helpful i.e., what are the predisposing, precipitating and maintaining factors in this person's symptoms? It can also be useful to think about how someone's symptoms may have a physiological (as opposed to patho-physiological) explanation.

Biological Factors

Genetics There is evidence that the general tendency to experience symptoms has a partly heritable basis (Gillespie, Zhu et al. 2000). Furthermore the evidence for the role of genetics in specific somatoform disorders has also increased in recent years. For example twin studies have shown that CFS/ME is substantially heritable (Buchwald, Herrell et al. 2001) and there is also evidence that chronic pain states, including fibromyalgia, might have a genetic component (Buskila, 2007), as might irritable bowel syndrome (Talley, 2006). There may be some genetic liability for hypochondriacal disorder and somatisation disorder, but this has been less investigated (Kendler, Walters et al. 1995; Noyes, Holt et al. 1997). Neuroendocrine changes

Changes within the neuroendocrine system offer an interesting explanation for some of the biological changes seen in the somatoform disorders, although the story is not totally

coherent. Most intensive research in this field has been done in CFS/ME and fibromyalgia. There is some evidence of low circulating cortisol in CFS/ME, which is in contrast to the pattern seen in major depression (Parker, Wessely et al. 2001; Cleare 2003). In addition the serotonergic system may be overactive in CFS/ME (Parker, Wessely et al. 2001). A reduction in the responsivity of the hypothalamic-pituitary-adrenal (HPA) axis has also been shown in fibromyalgia (Parker, Wessely et al. 2001). Neuroendocrine changes in irritable bowel syndrome have been less examined, although there is some evidence of abnormal activity of the HPA axis and also that the gut may be over activated by corticotrophin releasing hormone in those with the condition (Fukudo, Nomura et al. 1998). It is likely that at least some of the neuroendocrine abnormalities that have been observed are secondary and these abnormalities are probably best viewed as maintaining factors.

Infection or injury Injury and infection may play a precipitating role in some somatoform disorders and this idea has been most explored for conditions such as CFS/ME and fibromyalgia. In clinical practice patients often cite an injury as the precipitant to chronic pain conditions such as fibromyalgia and this has some limited support in the literature (Al-Allaf, Dunbar et al. 2002). It is generally accepted that there is no single infective agent involved in the pathogenesis of CFS/ME (Afari and Buchwald 2003) or irritable bowel syndrome (Talley and Spiller 2002). Prospective cohort studies - the only way to determine causality - have confirmed that exposure to Epstein-Barr virus (EBV) increases he risk of CFS/ME (White, Thomas et al. 1998), as have Q fever, Lyme Disease (Prins, van der Meer et al. 2006) and viral illnesses requiring hospitalisation (Hotopf, Noah et al. 1996). However, psychiatric morbidity, female gender and prolonged convalescence are still the most important predictors of developing CFS/ME following infection (Hotopf, Noah et al. 1996; Candy, Chalder et al. 2003).

As we write the world's media are reporting a great breakthrough in the struggle to identify the cause of CFS/ME; a new retrovirus (XMRV) has been identified in 67% of a large series of CFS/ME patients in the USA but only 3% of controls (Lombardi, Ruscetti et al. 2009) - an association that is stronger than that between smoking and lung cancer. The finding is contained in the journal Science, a peer reviewed journal of outstanding reputation. It is indeed genuinely exciting and if true will indeed represent perhaps the single most important change in our understanding of the illness so far. Clinical practice will indeed change, and in the not too distant future, new and novel treatments should emerge. Of course the findings may not stand up to scrutiny, and there have been other equally dramatic claims made in this field before, which have not stood the test of time and replication. But, assuming that this new breakthrough is indeed just that, does that mean that all previous knowledge about CFS is rendered obsolete? Not at all. Perhaps a new drug will abolish CFS, but that seems unlikely. There will remain a major role for the kind of understanding and interventions that are the focus of this chapter, just as they remain important in so many other illnesses and diseases.

Deconditioning Physical deconditioning offers an appealing mechanism for the maintenance of symptoms in the somatoform disorders. There is some evidence for reduced physical fitness in fibromyalgia (Valim, Oliveira et al. 2002) and reduced exercise capacity in CFS/ME when compared to sedentary controls (Fulcher and White, 2000). For patients with chronic and severe somatoform disorders (such as somatisation disorder) the physical effects of years of reduced activity or the use of aids such as wheelchairs can be profound. Such patients present an enormous rehabilitation challenge.

Central dysfunction Some preliminary neuroimaging studies have been conducted in conversion disorder, CFS/ME, irritable bowel syndrome and pain syndromes that suggest that central mechanisms may play a role in these disorders. For example several functional neuroimaging studies have suggested that inhibitory networks are abnormally activated in conversion disorder (Aybek, Kanaan et al. 2008). At present, the usefulness of neuroimaging research in somatoform disorders is limited, but taken as a whole probably does support the idea of aberrant patterns of brain activation in these conditions (particularly in response to relevant probes such as experimentally induced pain). It is not known whether these changes pre-exist the illness or have developed secondarily.

Psychological Factors

Childhood experiences Experience in childhood appears to be relevant to the development of somatoform disorders later in life. Longitudinal studies show that children who experience parental ill health in childhood are more likely to develop medically unexplained symptoms as adults (Hotopf, Mayou et al. 1999). Whether childhood illness increases the likelihood of adult somatoform disorders is less clear – certainly childhood medically unexplained illness appears to do so (Hotopf, Wilson-Jones et al. 2000). Childhood sexual abuse increases the risks of adult somatoform disorders (Paras, Hassan Murad et al. 2009).

Stressful events Stressful events can precipitate the onset of a somatoform disorder and are known to occur more frequently in the period leading up to the onset of medically unexplained symptoms (Craig, Drake et al. 1994). A similar picture has been shown for CFS/ME, with patients experiencing "dilemmas" in the months preceding onset (Hatcher and House, 2003). Chronic stress (or life events) has also been shown to be important in the onset and maintenance of symptoms in irritable bowel syndrome (Creed, Craig et al. 1988; Bennett, Tennant et al. 1998) and fibromyalgia (Anderberg, Marteinsdottir et al. 2000). Trauma such as sexual abuse (Paras, Hassan Murad et al. 2009) or involvement in a disaster (van den Bergh, Grievink et al. 2005) also appears to be a risk factor for the development of a range of somatoform disorders

Personality It is often presumed that personality factors are an important predisposing and maintaining factor in somatoform disorders, although there is little supporting evidence. Emotional instability (or neuroticism) may prolong the course of hypochondriacal disorder (olde Hartman, Borghuis et al. 2009) and, along with introversion, has been found to be a risk factor for the development of CFS/ME (Kato, Sulllivan et al. 2006; Prins, van der Meer et al. 2006). Patients with non-epileptic seizures (a type of conversion disorder) have been found to have high rates of personality disorder (Bowman and Markand, 1996). Clinically, patients with co-morbid personality disorder can be very challenging to manage.

Illness beliefs Illness beliefs are enormously important in the maintenance (and possibly precipitation) of somatoform disorders. Beliefs link bi-directly to both behaviours and emotions, which means that by altering one of these domains the other two are likely to be affected – see the diagram below. Patients with CFS/ME are more likely to make physical illness attributions for a selection of common symptoms compared to controls (Butler, Chalder et al. 2001); perhaps in consequence and are more likely to believe their illness will be chronic and have serious consequences when compared to patients with chronic medical conditions (Weinman, Petrie et al. 1996). Illness worry is related to disability in fibromyalgia, but not in rheumatoid arthritis (Robbins and Kirmayer, 1990). Likewise, those with irritable

bowel syndrome score more highly on hypochondriacal and bodily preoccupation scales than control groups (Gomborone, Dewsnap et al. 1995).

Making physical attributions for unexplained symptoms is natural – the problem is what these may imply for the person's concepts of self efficacy, acceptable treatment and likely prognosis. Deale et al showed that for patients with CFS to recover, it was not necessary that their illness attributions changed (e.g., "the illness is physical and caused by a virus"), but instead improvement was linked to change in beliefs such as "doing too much makes me worse," "I need to rest to get better" and so on (Deale, Chalder et al. 1998). In other words, physical illness attributions can act as a confounder or marker for more unhelpful beliefs that are associated with maladapative coping responses.

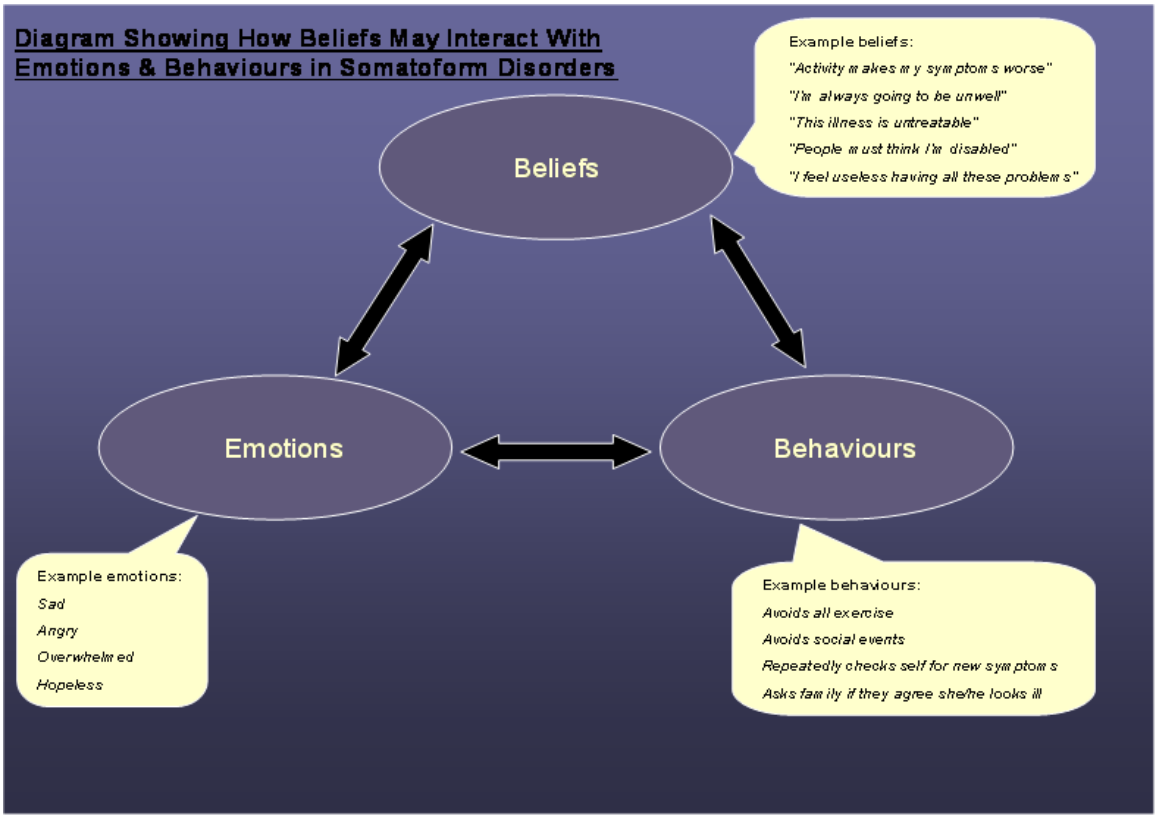

Figure 1

The term "symptom amplification" is used to describe the manner in which innocuous symptoms become incorrectly attributed and then incorporated into a patient's understanding of their illness, which leads to further incorrect attribution of other symptoms as they arise (Barsky and Borus, 1999). These beliefs and attitudes about symptoms may act as a mechanism that then guides the patient to adopt avoidant behaviours, leading to limitation of activity, which in turn leads to the secondary deconditioning and neuroendocrine effects outlined above. Avoidance behaviours are invariably based on the patient's understanding of their illness (e.g., "when I feel fatigued, I cause myself further harm if I exercise") and are often possible to work with during treatment (Deale, Chalder et al. 1998).

Socio-cultural Factors

Living Environment We have discussed above the possible importance of the early family environment in predisposing someone to suffer from medically unexplained symptoms (e.g., by experiencing the illness of a parent in early life), however the behaviour and attitude of close family and friends can also play a role in the maintenance of medically unexplained symptoms. For example partners of patients with CFS/ME are more likely to make physical attributions about their partner's symptoms than the partners of fracture clinic patients (Butler, Chalder et al. 2001). Clinically it is often as relevant to understand the illness beliefs of close family as it is the patient's – particularly when the family are providing high levels of care and support.

Financial Reward The financial "reward" to be gained from disability payments or litigation has been argued to play a role in the maintenance of ill-health in those suffering from somatoform disorders (Malleson, 2002). For example, being in receipt of sickness benefit or certification has been shown to be a poor prognostic sign in CFS/ME (Cope, David et al. 1994; Bentall, Powell et al. 2002) and fibromyalgia (Wigers, 1996), whilst the whiplash syndrome does not appear to exist in countries without an insurance/compensation culture (Schrader, Obelieniene et al. 1996).

Media Several functional somatic syndromes including CFS/ME, Gulf War syndrome and repetitive strain injury, have gained public credibility in spite of widespread medical scepticism as to their very existence. The role of the media in this process has often been highlighted (Shorter, 1995; Barsky and Borus, 1999; Hazemeijer and Rasker, 2003). The availability and explosion in internet sites has also meant that patients may inadvertently be exposed to information that is inaccurate or even harmful (Armstrong, 2000; Kisely, 2002).

Treatment

The assessment itself can be therapeutic, particularly if time is taken to provide a clear explanation for symptoms, which is not perceived by the patient to blame them. The doctor may need to avoid colluding with the patient, but also avoid denying the reality of the symptoms. Research has shown that "empowering" explanations are the most beneficial for patients with medically unexplained symptoms (i.e., explanations that provide a tangible mechanism, de-emphasise blame and provide the opportunity for self-management) (Salmon, Peters et al. 1999). The provision of clear information in different forms (i.e., verbal and written) is necessary. Patients with medically unexplained symptoms often appear to be seeking reassurance, but this can be difficult to deliver effectively. It is counter-productive to tell a patient that "there is nothing wrong," when their symptoms are proof that there is. On the other hand it is important to counter specific illness fears that the patient may hold (e.g., "My symptoms mean I've got cancer," "This rash shows that I have HIV," "If I do too much I will permanently damage my spine") if that is not the case. This is why it is important to have asked the patient what they believe is wrong. Patients with hypochondriacal disorder will often attempt to elicit repeated reassurance, which fails to provide reassure for any length of time (Deale, 2007).

If there is evidence of anxiety or depression at first assessment, then this should be treated in the usual way. Doing so will often, although not always, lead to a significant improvement

in the patient's somatic symptoms. A doctor that sees a patient with medically unexplained symptoms for follow-up has an important role to play in managing that patient's interaction with medical services. Even if the doctor does not perceive themselves to be providing active therapy, they can be aware of potentially iatrogenic interventions (i.e., harm caused by doctors) (Page and Wessely, 2003). They can also provide regular follow-up that is not contingent on the patient being symptomatic, thereby discouraging the need for the patient to complain of symptoms in order to elicit care. It is sometimes possible to agree beforehand that only a certain proportion of the session will be devoted to discussing symptoms, and leave it to the patient to decide the content of the second half of the interview.

Psychotherapy

Overall cognitive behavioural therapy (CBT) is known to be an efficacious treatment for the range of the conditions loosely grouped under the somatoform disorders (Sumathipala, 2007). CBT and similar therapies have shown specific usefulness in the treatment of hypochondriacal disorder (Thomson and Page, 2007), CFS/ME (Chambers, Bagnall et al. 2006), irritable bowel syndrome (Brandt, Bjorkman et al. 2002), fibromyalgia (Rossy, Buckelew et al. 1999) and burning mouth syndrome (Zakrzewska, Glenny et al.). CBT can be adapted for use in any of these disorders, but like most medical treatments relies on the patient being sufficiently motivated to participate. One of the first goals in CBT is for the therapist and patient to come to a shared understanding of the patient's problems using a CBT framework – the therapist often uses diagrams like the one on page 18 to illustrate this. Evidence is lacking for useful psychotherapeutic treatments for conversion disorder (Martlew, Baker et al. 2007), although preliminary studies have shown that, once again, CBT may be useful (Goldstein, Deale et al. 2004).

Pharmacotherapy

Overall there is evidence that antidepressant medication is useful in the treatment of somatoform disorders (O'Malley, Jackson et al. 1999; Sumathipala, 2007), although it is not possible to generally recommend the use of one type of antidepressant over another. For the functional somatic syndromes there are some specific recommendations, for example tricyclic antidepressants are effective in treating fibromyalgia (Arnold, Keck et al. 2000), abdominal pain in irritable bowel syndrome (Brandt, Bjorkman et al. 2002) and premenstrual tension (Steiner, Steinberg et al. 1996). On the other hand antidepressants have not been found to be useful in CFS/ME without co-morbid depression (Whiting, Bagnall et al. 2001). In general the effectiveness of antidepressants in these disorders increases if the patient has evidence of co-morbid depression or anxiety, however medication is probably less effective than psychological approaches.

It can be necessary to rationalise inappropriate medication, as some patients with somatoform disorders are prescribed medication that is unnecessary or even harmful. This needs to be done by (or in conjunction with) primary care and the rationale discussed with the patient in advance.

Combined treatments

In clinical practice it is common to combine a psychotherapeutic and pharmacological approach to management. The patient may have strong feelings about treatment and

these should be taken into consideration. In developed countries treatment for somatoform disorders can sometimes be provided by specialists (e.g., consultation-liaison psychiatrists) attached to general hospitals, although provision is often patchy and as in developing countries much of the burden falls to primary care.

Final Considerations

Factitious disorder or Munchausen's syndrome is listed separately (adjacent to the somatoform disorders) in DSM-IV classification, whilst ICD-10 classes it amongst the personality disorders. Malingering is not considered to be a psychiatric disorder by either system. However the distinction of factitious disorder or malingering from the somatoform disorders can be unclear, so for the sake of completeness we mention them here. Diagnostic features are outlined below. Factitious disorder is probably a rare condition about which little is known, although persons suffering from this disorder are likely to have significant personality disturbance and a background of neglect or abuse. Malingering is more common, although quite how common is unknown due to the nature of the behaviour.

Factitious disorder

• Persistent faking of symptoms or self-infliction of wounds to produce symptoms • Persistent visits to hospital in order to gain care for these symptoms (may move from hospital to hospital to avoid detection) • No external gain (e.g., financial) is apparent, so the gain is viewed as being psychological

Malingering

• Deliberate falsification of a medical condition • The falsification (or exaggeration) is for financial or other obvious material gain

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5 Dissociative Disorders

5.1 Introduction

Dissociative disorders are a fascinating group of disorders which is considered a myth by some and by some, a reality. Dissociation is defined as a disruption in the usually integrated functions of consciousness, memory, identity and perception of the environment (Mulder et al. 1998) leading to a fragmentation of the coherence, unity and continuity of the sense of self. Dissociative disorders were first officially classified as a separate diagnostic group in DSM-III (Tutkun et al. 1998). Besides being a disorder on its own, dissociation may accompany several psychiatric disorders as a confounding factor or co morbid disorder (Evren et al. 2007). Dissociative disorders may accompany several psychiatric disorders (Sar & Ross, 2006) including borderline personality disorder (Sar et al. 2003; Sar, Akyuz, Kugu, Ozturk, & Ertem-Vehid, 2006), obsessive–compulsive disorder (Lochner et al. 2004), posttraumatic stress disorder (Briere, Scott, & Weathers, 2005), acute stress disorder (Spiegel, Classen, & Cardena, 2000), eating disorders (Farrington et al. 2002), pathological gambling (Grant & Kim, 2003), kleptomania (Grant, 2004), and schizophrenia (Ross & Keyes, 2004). Traumatic childhood experiences play a major role in the development of dissociative disorders (Tutkun et al. 1998; Kluft, 1991; Spiegel, 1991). Regression analysis done in one of the studies indicated that dissociation in young adulthood was significantly predicted by observed lack of parental responsiveness in infancy, while childhood verbal abuse was the only type of trauma that added to the prediction of dissociation (Dutra et al. 2009). Substance use is suggested to be an important problem among patients with dissociative disorder (Evren et al. 2007; Ellason et al. 1996).

Other conditions that can mimic similar symptoms as dissociative disorders are Dementia, Substance induced, certain medical conditions such as Multiple sclerosis, temporal lobe epilepsy, head trauma and other psychiatric conditions such as Post Traumatic Stress Disorder, somatoform disorders, affective illnesses, anxiety disorders as well as malingering (Chu et al. 2005).

This chapter gives an overview of Dissociative disorders including clinical symptoms and classification, pathogenesis and management (assessment and treatment).

5.2 Phenomenology

5.3 Epidemiology

Several studies have shown that dissociative disorders may have been previously under diagnosed and a much higher prevalence is encountered. (Foote et al. 2006) The prevalence

of dissociative disorders in general psychiatric settings ranges between 5.0% and 20.7% among inpatients (Sar et al. 2007) and between 12.0% and 29.0% among outpatients. (Sar et al. 2007) In an outpatient study (the only methodologically strong outpatient study) in Turkish outpatients Sar et al. found that 12% of Turkish outpatients could qualify for a diagnosis of a dissociative disorder, including 4% with dissociative identity disorder and 8% with dissociative disorder not otherwise specified. (Foote et al. 2006) Only 1% of those patients had been diagnosed with dissociative disorder before entering the study. (Foote et al. 2006) Inpatient populations have been studied more thoroughly as listed in Table 1. (Foote et al. 2006) In one of the studies, frequency of dissociative disorders was studied in the psychiatry emergency ward and noted to be as high as 34.9%. (Sar et al. 2006)

Table 1. Studies of the prevalence of dissociative disorders in inpatient psychiatric patients

Study	Patients with Dissociative disorder (%)	Patients with Dissociative Identity disorder (%)
Ross et al.	21	3-5
Saxe et al.	13	4
Horen et al.	17	6
Latz et al.	15	4
Knudsen et al.	8	5
Lussier et al.	9	7
Tutkun et al.	10	5
Rifkin et al.	?	1
Friedl and Draijer	8	2
Gast et al.	4-8	1-2

5.4 Clinical Symptoms and Classification

In International Classification of Diseases, 10th revision (ICD-10) dissociative disorders has been listed under the category of Neurotic, stress- related and somatoform disorders. It includes conversion, hysteria and hysterical psychosis and excludes malingering. As per ICD-10, in dissociative disorders there is a partial or complete loss of the normal integration between memories of the past, awareness of identity and immediate sensations, and control of bodily movements. They are presumed to be psychogenic in origin, being associated closely in time with traumatic events, insoluble and intolerable problems, or disturbed relationships. The symptoms cannot be attributed to any medical or neurological disorder excluded by physical exam and investigations. In addition, there is evidence that the loss of function is an expression of emotional conflicts or needs.

Table 2. Classification and clinical symptoms of dissociative disorders (F44) as per ICD-10 criteria

ICD-10 Code	Classification	Symptoms	Excludes

ICD-10 Code	Classification	Symptoms	Excludes
F44.0	Dissociative amnesia	Loss of memory, usually of important events, not due to organic disorder or ordinary fatigue/forgetfulnessCentered on traumatic events e.g., accidents or unexpected bereavements	Psychoactive substance induced amnesic disorder-NOSAnterograde, retrograde amnesiaNonalcoholic organic amnesic syndromePostictal amnesia in epilepsy
F44.1	Dissociative fugue	Symptoms of dissociative amnesia + purposeful travel beyond the usual everyday range.	Postictal fugue in epilepsy
F44.2	Dissociative stupor	Profound diminution or absence of voluntary movement & normal responsiveness to external stimuli such as light, noise & touch.Evidence of recent stressful event(s).	Organic catatonic disorderStupor: • NOS • Catatonic • Depressive • manic
F44.3	Trance & Possession disorders	Temporary loss of the personal identity & full awareness of the surroundings.Involuntary or unwanted.	States associated with: • acute & transient psychotic disorders • organic personality disorder • postconcussional syndrome • psychoactive substance intoxication • schizophrenia
F44.4	Dissociative motor disorders	Loss of ability to move the whole or a part of a limb or limbs (most common).AphoniaDysphonia	

ICD-10 Code	Classification	Symptoms	Excludes
F44.5	Dissociative convulsions	Epileptic seizures like movements but with maintenance of consciousness or replaced by a state of stupor or trance.Tongue biting, urinary incontinence, bruising due to falling are rare.	
F44.6	Dissociative anaesthesia and sensory loss	Anaesthetic areas of skin not corresponding to dermatomal distribution.Sensory loss not explained by any neurological lesion; may be accompanied with paresthesia.Psychogenic deafness.	
F44.7	Mixed dissociative (conversion) disorders	Combination of disorders specified in F44.0-44.6	
F44.8	Other dissociative disorders	Ganser's syndrome-Multiple personalityPsychogenic • confusion • twilight state	
F44.9	Dissociative (conversion) disorder, unspecified		

The DSM-IV-TR talks about dissociative amnesia and fugue as part of dissociative disorders as included in the ICD-10 criteria but conversion disorder is a part of Somatoform disorders rather than dissociative disorders in the DSM-IV. Dissociative stupor, trance, convulsions, Ganser syndrome and motor disorders are all grouped together under Dissociative disorder NOS rather than being classified separately as in ICD-10. Dissociative Identity disorder, formerly known as multiple personality disorder is sub-classified as a part of "Other dissociative disorders" in ICD-10 whereas it has been classified separately in the DSM-IV. The American Psychiatric Association's DSM-IV recognizes dissociative disorders as official diagnostic category; by contrast World Health Organization's ICD-10 is more skeptical classifying dissociative disorders as conversion disorders and suggesting the dissociative identity disorder may be "a culture-specific or even iatrogenic condition." (Lalonde et al.

2001) No matter what the differences are in the classification, the overall suggestibility of the symptoms and signs are the same and the same methods of assessment may be used to diagnose dissociative disorders.

5.5 Assessment

The first step is to do a detailed clinical interview including questions about significant childhood and adult trauma. Clinicians should use careful clinical judgment about how much detail of traumatic experiences to pursue during initial interviews, especially when those experiences seem to be poorly or incompletely remembered. A premature trauma anamnesis may evoke a florid decompensation (Chu et al. 2005). The patient should be asked about episodes of amnesia,fugue, depersonalization, derealization, identity confusion, and identity alteration, age regressions, autohypnotic experiences, hearing voices, passive-influence symptoms such as "made" thoughts, emotions, or behaviors and somatoform symptoms such as bodily sensations related to past trauma (Chu et al. 2005).

5.5.1 Measures of Dissociation

There are three classes of instruments that assess dissociation:

Clinician-administered structured interviews, clinician-administered measures, and self-report instruments (Chu et al. 2005).

Clinician-administered structured interviews

The Structured Clinical Interview for DSM-IV Dissociative Disorders-Revised (SCID-D-R) (Bremner et al. 1993) is a 277-item interview that assesses five symptoms of dissociation: amnesia, depersonalization, derealization, identity confusion, and identity alteration. The SCID-D-R has good-to-excellent reliability and discriminant validity.

The Dissociative Disorder Interview Schedule (DDIS) is a 132-item structured interview with a yes/no format that assesses the symptoms of the five DSM-IV dissociative disorders, somatization disorder, borderline personality disorder, and major depressive disorder. The DDIS also assesses substance abuse, Schneiderian first-rank symptoms, trance, childhood abuse, secondary features of Dissociative Identity Disorder, and supernatural/paranormal experiences.

Clinician Administered Measures

The Clinician Administered Dissociative States Scale (CADSS) (Bremner et al. 1998) has 27 items with 19 subject-rated items and 8 observer-scored items, all rated on a 0-4 scale. It has three factors that assess symptoms of amnesia, depersonalization and derealization.

Self-Report Instruments

There are six self-report measures of dissociation that have been used with some frequency (Chu et al. 2005): the Dissociative Experiences Scale [DES], the Questionnaire of Experiences of Dissociation [QED], the Dissociation Questionnaire [DIS-Q], Somatoform Dissociation Questionnaire [SDQ] and the Multiscale Dissociation Inventory [MDI])

Dissociative Experiences Scale (DES, Bernstein and Putnam, 1989)

The Dissociative Experiences Scale is a widely used 28-item self-report measure for assessment of specific dissociative experiences (Bernstein et al. 1986, Carlson et al. 1993).Items are rated on a continuous scale (original version) or on an11-point Likert scale (revised version) that ranges from 0 ("never") to100 ("always"). DES items primarily tap absorption, imaginative involvement, depersonalization, derealization, and amnesia (Chu et al. 2005).

The Questionnaire of Experiences of Dissociation (QED; Riley, 1988) is a 26-item, true/false self-report instrument-not very frequently used (Chu et al. 2005).

The Dissociation Questionnaire (DIS-Q; Vanderlinden, Van Dyck,Vandereycken, Vetommen, & Verkes, 1993; Vanderlinden, 1993) is a 63-item, five-point Likert format, self-report instrument-commonly used in Europe (Chu et al. 2005).

The Somatoform Dissociation Questionnaire-20 (SDQ-20) is a 20-item self-report instrument using a five-point Likert scale (Nijenhuis, Spinhoven,Van Dyck, Van der Hart, & Vanderlinden, 1996). The SDQ-20 is explicitly conceptualized as a measure of somatoform dissociation.

The Multidimensional Inventory of Dissociation (MID) is a 218-item self-report, multiscale measure of pathological dissociation that makes diagnoses and yields a comprehensive dissociative profile (Dell, 2004). The MID is the only measure of dissociation that has validity scales: Defensiveness, Rare Symptoms, Attention-Seeking Behavior, Factitious Behavior, and Neurotic Suffering (Chu et al. 2005)

The Multiscale Dissociation Inventory (MDI; Briere, 2002) is a 30-item multiscale measure of dissociation with a 5-point Likert format. The MDI is fully standardized, allowing t score comparisons to anormative group of trauma-exposed men and women. It yields six subscales–Disengagement, Depersonalization, Derealization, Emotional Constriction/Numbing, Memory Disturbance, and Identity Dissociation–and a total dissociation scale (Chu et al. 2005).

5.5.2 Other Psychological Tests

Along with more specific diagnostic testing (e.g., SCID-D-R, DES, etc.), standardized psychological tests (MMPI-2, Rorschach etc.) may aid the clinician in differential diagnosis and prognosis, the identification of co-morbid disorders, and the evaluation of treatment options (Chu et al. 2005).

5.5.3 Special investigations

No specific investigations are specific to Dissociative disorders. In one study, MRI revealed the amygdalar and hippocampal volumes to be smaller in females with Dissociative identity

compared to healthy subjects (Vermetten et al. 2006). But the use of such expensive studies such as MRI is questionable to diagnose dissociative disorders, also when this finding is not specific to dissociative disorders. In another study it was documented that low serum lipid levels may be related to a high incidence of self-injurious behaviors and borderline features in patients with dissociative disorders (Agargun et al. 2004).

5.5.4 Other rating scales that are available for use to assess Dissociative disorders (http://www.neurotransmitter.net/dissociationscales.html)

Diagnostic Drawing Series (DDS) (Mills & Cohen, 1993 Adolescent Dissociative Experiences Scale-II (A-DES) Child Dissociative Checklist (CDC), Version 3 Peritraumatic Dissociative Experiences Questionnaire (PDEQ) Cambridge Depersonalization Scale Steinberg Depersonalization Questionnaire Adolescent MID 6.0 Dissociative Features Profile (DFP)

5.6 Pathogenesis

The research regarding etiology of Dissociative Disorders is controversial. Several factors make it difficult to perform, especially the high co-morbidity of Dissociative Disorders with other psychiatric pathologies. The dissociation may be observed as a transient phenomenon secondary to a medical condition such as temporal lobe epilepsy (Bob, 2007). In addition, dissociative symptoms may be a part of the symptomatology of Substance Abuse, Borderline Personality Disorder, or Obsessive Compulsive Disorder. Some researchers even argue that Dissociative Disorders don't exist as separate diagnoses at all and should be considered a part of post-traumatic psychopathology. As a general consensus, a link between dissociative symptoms in adulthood and self-reports of childhood traumatic events (including familial loss in childhood, sexual/physical abuse and neglect) has been documented.

5.7 Biological Factors

GENETICS

To date, not many studies have been done to determine the genetic predisposition to Dissociative Disorders. Results of existing studies confirm that the dissociation may be partially genetically determined, although results of twin studies are controversial. One study, by Waller, 1997, found no evidence and another study, by Jang, 1998, found 48% to 55% genetic influence. A study by Savitz, 2008, found that there is involvement of COMT Val158Met polymorphism in mediating the relationship between pre-existing trauma and following development of dissociative psychopathology.

NEUROBIOLOGY

In the area of neurobiological research, multiple studies were done that confirm the presence of physiological changes associated with dissociative symptoms. As already mentioned, there is a hypothesis that early psychological trauma or abuse (i.e., stress) can mediate the development of those changes. To date, several neurotransmitter systems have been

implicated in the development of Dissociative Disorders: Hypothalamo-Pituitary-Adrenal Dysfunction (HPA), Glutamate/N-methyl-D-aspartate (NMDA) receptor, Serotonin 5-HT2a, 5-HT2c, ?-aminobutyric acid (GABA), and Opioid receptors.

The HPA axis is known to play a central role in medicating the stress response. Several studies on this have been done to date. Most of them presented similar findings showing that individuals with dissociative symptoms have basal HPA-axis hyperactivity with elevated cortisol and diminished pituitary negative-feedback inhibition (Simeon, 2006).

As an extension of this dysregulation due to stress, some research was performed using neuroimaging. In both animal and human studies, stress at a young age has been shown to be associated with changes in the structure of the hippocampus. Smaller hippocampal and amygdalar volumes in patients with dissociative symptoms have been reported by some researchers (Vermetten, 2006). Decreased hippocampal volume may be explained by stress exposure; the hippocampus is a major target organ for glucocorticoids, which are released during stressful experiences, and prolonged exposure to glucocorticoids can lead to progressive atrophy of the hippocampus. The exact mechanism that can lead to smaller amygdalar volume is unclear. It is possible that other neurotransmitters play a role in this change. In their study, D'Souza et al. (2006) proposed that dissociative symptoms, similar to psychosis, may be related to the inhibitory (GABAergic) deficits that cause unopposed stimulation of serotonin receptors. Lysergic acid diethylamide (LSD), dimethyltryptamine (DMT) work as agonists of serotonin 5-HT2a and 5-HT2c receptors, again suggesting a possible mediating role for serotonin in dissociation.

A similar mechanism might underlie cognitive effects of NMDA receptor antagonists, such as ketamine, which was found to cause a profound dissociative state in healthy individuals. NMDA receptors are widely distributed in the cortex, as well as in the hippocampus and the amygdala; therefore, it is possible that diminished NMDA-related neurotransmission may be related to dissociative states. The effect of cannabinoids confirm this hypothesis, as they have been shown to block NMDA receptors at sites distinct from other noncompetitive NMDA antagonists (Feigenbaum, 1989) and still cause dissociative symptoms.

Several studies using positron emission tomography have been performed. One showed that depersonalization severity was correlated with an increase in cerebral blood flow (CBF) in the right frontal cortex and anterior cingulate, and a decrease in subcortical flow in the amygdala, hippocampus, basal ganglia and thalamus (Mathew, 1999). Reinders (2006) found psychobiological differences for the different dissociative identity states. Regional cerebral blood flow (rCBF) data revealed different neural networks to be associated with different processing of the neutral and trauma-related memory script. Sar et al. (2001, 2007) demonstrated decreased bilateral perfusion in frontal and occipital regions among patients with dissociative identity disorder (DID) compared with a group of non-traumatized healthy individuals, which the researchers think provides some validation of the existence of dissociative identity disorder as a distinct diagnostic category. These results also confirm the "orbito-frontal model" of Dissociative Identitiy Disorder proposed by Forrest (2001), which hypothesizes that the orbito-frontal cortex plays a critical role in the development of dissociative identities due to its inhibitory function. Research regarding the neurobiology of dissociative disorders is ongoing and continues.

5.8 Psychological Factors

There is growing interest in the role of early childhood disturbances of attachment and parenting in the development of dissociation (Dutra, 2009). From that article: "Bowlby, in 1973, suggested that infants may internalize dissociated or unintegrated internal working models of their primary caretakers, as well as of themselves. Main and Solomon (1990) then documented the existence of contradictory, confused, and disoriented behavior among some infants in the presence of the parent when needing comfort. These were termed disorganized/disoriented attachment behaviors. Subsequent meta-analyses have confirmed the association between infant disorganized attachment behavior, parental maltreatment, parental psychopathology, disturbed parent-infant interaction, and childhood behavior problems (Madigan et al. 2006; van IJzendoorn et al. 1999). Liotti (1992) further noted that there are suggestive parallels between infant disorganization and adult dissociation in that both phenomena reflect a pervasive lack of mental or behavioral integration." As discussed above in the "Biological Factors" section, early childhood trauma, loss or abuse are strongly correlated with the development of dissociative symptom. Along with the traumagenic theory of development of dissociative disorders, especially Dissociative Identity Disorder (DID), there are iatrogenic and pseudogenic positions (Reinders, 2006). The iatrogenic position takes the view that Dissociative Identity Disorder symptoms are often induced during psychotherapeutic treatment where there is good therapeutic alliance, high therapeutic dependency and high suggestibility. Therapy may contribute to the creation of false memories, and then separate and distinct identities, leading to the creation of Dissociative Identity Disorder phenomena. Laney and Loftus (2005) and Loftus and Davis (2006) describe cases where individuals that claimed to be amnestic had false memories that were "reconstructed" during therapy. Pseudogenic Dissociative Identity Disorder includes subjects who are simulating DID without any therapeutic intervention. It is a conscious process used for achieving secondary gain.

5.9 Social/Cultural Factors

CULTURAL FACTORS

There is a growing body of research targeted at possible cultural differences, significance of the place of origin or other ethnical background in the development of dissociative disorders. Racial and ethnic differences were studied by Douglas (2009) in a non-clinical population and the results indicated differences in dissociation as a function of race: Africans and Asian Americans reported significantly higher rates of dissociation compared to Whites. A substantial proportion of recently published cases of dissociative disorders showed that immigration is an important factor in the development of DID (Staniloiu, 2009). Fatalism, trance, possession, spiritual and healing practices (Seligman, 2008; Moreira-Almeida A, 2008) are being studied. All this research can advance the ethnographic studies of dissociation and highlights the importance of social and cultural aspects of its development.

JURISPRUDENCE

One of the social aspects of debate is implication of DID in jurisprudence. This illustrates how iatrogenic and pseudogenic theories of development DID may be implicated. There are

three categories of legal complications related to the diagnosis of dissociative disorders that the court system has to deal with (Reinders, 2006). Firstly, the individual suffering from DID may accuse another person of sexual or physical abuse. Secondly, the individual suffering form DID may claim not to be responsible for crimes committed in a different identity state. And, thirdly, if a person has multiple identities, which one can legally represent that person?

FAMILIES

To date, several family environmental factors were found to be associated with dissociation, including lack of parental care and warmth (Mann and Sanders, 1994; Modestin et al. 2002), inconsistent discipline (Braun and Sachs, 1985; Mann and Sanders, 1994), and poor relationship between parents (Maaranen et al. 2004). Additionally, all of these factors were also associated with abusive environments (Wolfe, l985). Familial and social support should be recognized as important protective factors against the development of DID (Korol, 2008).

5.10 Treatment

In treating patients with Dissociative Disorders, a variety of theoretical approaches are reported to be effective including cognitive behavioral therapy, hypnosis, psychopharmacological treatment, psychodynamic therapy, phenomenological treatment, contextual treatment, cognitive analytic therapy, feminist-informed treatment, and adjunctive treatment with Eye Movement Desensitization and Reprocessing (Brand et al. 2009). However, a review of the current literature examining the treatments for Dissociative Disorders illustrates a serious lack of well-designed studies on the treatment of Dissociative Disorders and a scarcity of controlled outcome research for Dissociative Disorder patients (Brand et al. 2009). A majority of the current information available regarding treatment recommendations for Dissociative Disorder is based off clinical and empirical evidence from case studies and case series. Although there are multiple approaches for treating Dissociative Disorders, the common element of these treatments addresses the dissociative pathology and exploring prior traumatic events. Treatment of Dissociative Disorders is associated with improvements in symptoms of dissociation, depression, general distress, anxiety and PTSD, as well as decreased use of medications and improved work and social functioning (Brand et al. 2009). Duration of treatment varies depending on the particular Dissociative Disorder being treated, with Dissociative Amnesia and Dissociative Fugue recovering more quickly and having a better outcome as compared to Dissociative Identity Disorder and Depersonalization Disorder. However, a significant proportion of patients' improvement during initial treatment may not remain stable over time, indicating the need for additional follow up for contingent intervention in the case of recurrent dissociative symptoms or other psychopathological states (Jans et al. 2008).

5.11 Psychotherapy

Overall, the most common form of treatment for the Dissociative Disorders is psychotherapy, which generally focuses on the dissociative psychopathology and associated trauma or stressor. Many different types of psychotherapy have been used in the treatment of Dissociative Disorders, including psychodynamic, cognitive behavioral, supportive, hypnotherapeutic, free

association and drug assisted. Dissociative Disorder patients often present with challenging symptomatology and one must be flexible in the approach and technique applied (Turkus and Kahler, 2006). It is crucial to recognize the devastating effects that the past trauma or stressor has had on the patient's life and their current state of dysfunction (Turkus and Kahler, 2006). Applying skill-building interventions at the beginning stages of treatment helps stabilize the patient and ameliorate the disabling dissociative symptoms, allowing treatment to progress and help patients to cope with painful affect and recollections of the traumatic experience (Turkus and Kahler, 2006). As psychotherapeutic techniques are applied in treatment, it is important to remember not to overwhelm the patient by forcing the intervention or insisting on following a preset time length for the treatment process as each patient's progress may vary. Patients with Dissociative Amnesia and Dissociative Fugue generally recover more quickly, especially when the dissociative event is of short duration, and their symptoms may even resolve spontaneously when the individual is removed from the precipitating trauma or stressor. However, longer-lasting episodes become more difficult to treat and may be intractable (Stern et al. 2008). Clinicians should try to restore patients' memories to consciousness as soon as possible; otherwise, the repressed memory may form a nucleus in the unconscious mind around which future dissociative episodes may develop (Sadock and Sadock, 2007). Treatment of Dissociative Amnesia is aimed at the restoration of missing memories while treatment of Dissociative Fugue is focused on the recovery of memory for identity and events preceding the fugue. Cognitive and psychodynamic are the most common psychotherapy techniques applied in treatment of Dissociative Amnesia and Dissociative Fugue; however, hypnotherapy and pharmacologically facilitated interviews are frequently necessary adjunctive techniques to assist with memory recovery (Sadock and Sadock, 2007).

In treating patients with Dissociative Identity Disorder, extended psychotherapy remains the treatment of choice, although approaches vary widely and remain controversial (Stern et al. 2008). Successful psychotherapy requires the clinician to be comfortable with a range of psychotherapeutic interventions (psychoanalysis, psychodynamic therapy, cognitive therapy, behavioral therapy, hypnotherapy, etc.) and be willing to actively work to structure the treatment (Sadock and Sadock, 2007). Comfort with family treatment and systems theory is helpful in working with a patient who subjectively experiences himself or herself as a complex system of selves with alliances, family-like relationships and intragroup conflicts (Sadock and Sadock, 2007). Some clinicians approach treatment by delineating and mapping the alternate identities, inviting each to participate in the treatment, and facilitating communication between the various identities in an attempt to understand past episodes of trauma as experienced by each identity (Stern et al. 2008). Other clinicians focus on the function of the dissociative process in the here-and-now of the patient's life and the ongoing treatment (Stern et al. 2008). They help patients become aware of using dissociation to manage feelings and thoughts within themselves and to manage the closeness and distance within relationships (Stern et al. 2008). All approaches seek to increase affect tolerance and to integrate the dissociated states within the patient (Stern et al. 2008). Patients with Dissociative Disorder who integrated their dissociated self states were found to have reduced symptomatology compared with those who did not integrate (Brand et al. 2009).

Treatment of Depersonalization Disorder is difficult and patients are often refractory to interventions (Stern et al. 2008). A variety of psychotherapeutic techniques can be used to treat Depersonalization Disorder, although none of these have established efficacy (Simeon, 2004). Treatment of accompanying psychiatric conditions (such as depression or anxiety)

may help and, as with other dissociative disorders, exploration of prior traumatic events may prove useful (Stern et al. 2008; Simeon, 2004).

5.12 Pharmacotherapy

Overall, the use of pharmacotherapy in the treatment of Dissociative Disorders is limited and controversial, as most medications (such as antidepressants and anxiolytics) are initiated to alleviate comorbid anxiety and mood symptoms, but do not treat the dissociative psychopathology. Currently, no pharmacological treatment has been found to reduce dissociation, per se (Stern, Rosenbaum et al. 2008). Although antidepressant medications are useful in the reduction of depression and stabilization of mood, one must be cautious in using benzodiazepines to reduce anxiety as they can also exacerbate dissociation (Sadock and Sadock, 2007; Stern, Rosenbaum et al. 2008). Presently, no specific pharmacotherapy exists for the treatment of Dissociative Amnesia and Dissociative Fugue other than pharmacologically facilitated interviews. A variety of agents have been used for this purpose, including sodium amobarbital, thiopental, benzodiazepines and amphetamines (Sadock and Sadock, 2007). This procedure is generally used for more acute cases, but can be occasionally useful in refractory cases of chronic dissociative amnesia when patients are unresponsive to other interventions (Sadock and Sadock, 2007). The material uncovered in a pharmacologically facilitated interview needs to be processed by the patient in his or her usual conscious state. In treating patients with Dissociative Identity Disorder using pharmacotherapy, there are reports of some success with selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, ?-blockers, clonidine, anticonvulsants, and benzodiazepines in reducing intrusive symptoms, hyperarousal, anxiety and mood instability (Sadock and Sadock, 2007; Stern, Rosenbaum et al. 2008). Atypical antipsychotics have also been used for mood stabilization, overwhelming anxiety and intrusive PTSD symptoms in patients with Dissociative Identity Disorder, as they may be more effective and better tolerated than typical antipsychotics. Although not routinely used, other possible suggestions for pharmacologically treating Dissociative Identity Disorder include the use of prazosin in reducing nightmares, carbamazepine to reduce aggression, and naltrexone for amelioration of recurrent self-injurious behaviors (Sadock and Sadock, 2007).

With regards to pharmacotherapy for Depersonalization Disorder, no medication has been shown to be efficacious to date, although research has been limited, and thus no definitive medication treatment guidelines exist (Simeon, 2004). Previous studies had suggested a possible role for serotonin reuptake inhibitors in treating primary Depersonalization Disorder, but unfortunately a more recently completed placebo-controlled trial, failed to show benefit with fluoxetine in 54 patients with Depersonalization Disorder (Simeon, 2004). As with the other Dissociative Disorders, treatment of comorbid anxiety and mood instability with antidepressants and anxiolytics may be useful.

5.13 Combined Treatment

Although psychotherapy is the most common and efficacious treatment approach for treating the Dissociative Disorders, it is not uncommon to combine psychotherapeutic technique and

pharmacological management in clinical practice. Reducing the patients' comorbid anxiety and mood instability with antidepressants and anxiolytics may help stabilize the patient overall and allow psychotherapy to progress, as well as help patients cope with painful affect and recollections of the traumatic experience as they arise.

5.14 Special Populations

Dissociative disorders can be a difficult set of disorders to diagnose due to their significant comorbidities and overlap with other psychiatric and medical diagnoses. Studies show a range of inpatient prevalences of 5% to 21% with outpatient prevalences ranging from 12% to 29%, which highlights the difficulty in accurate diagnosis (Brand et. al 2009). Dissociative disorders are shown to have significant comorbidity with multiple other psychiatric disorders that should be screened for including depression, borderline personality disorder, social anxiety, and somatization disorders (Evren et. al 2007) (Evren et. al 2009). More research needs to be done with dissociative populations to draw more firm conclusions, but many correlations have been gathered. Special populations that should be considered in relation to dissociative disorders include suicidal/self-mutilating, traumatized, eating disordered, substance abusing, and pediatric groups.

5.15 Suicidal and Self-Mutilating Populations

Both suicide attempts and self-mutilating behavior fall into the broader category of self-harm. While the difference between a suicidal or parasuicidal (self-mutilating) action may not always be easy to distinguish clinically, by definition they are quite distinct. Self-mutilation involves self-harm with no goal of suicide, while suicidal actions are meant to bring about one's death.

There is a fair amount of evidence supporting a relationship between dissociative disorder and suicide ideations/attempts. In one study of drug dependent patients there is a statistically significant increase in suicide attempts when comparing patients with dissociative disorder diagnoses to those without them (Tamar-Gurol et al. 2008). Another study showed that among patients with multiple suicide attempts, dissociative disorders are the strongest predictors of multiple suicide attempts when compared with borderline personality disorder, posttraumatic stress disorder, and alcohol abuse/dependence (Foote et al. 2008). With frequent comorbidity, there can be significant overlap between dissociative disorders, other psychiatric disorders, and suicidal behaviors. While there appears to be a link between dissociative disorders and suicidal ideations, a comorbid diagnosis of somatization disorder with dissociative disorder is a significant predictor of suicidal ideation (Ozturk and Sar, 2008). While suicidal behavior can be present in each specific dissociative disorder, it is particularly prevalent in Dissociative Identity Disorder possibly due to decreased affect tolerance (Kaplan and Sadock, 2007).

While self-mutilation and suicide attempts are distinct entities, nearly 55% to 85% of people with self-mutilating behavior have made a suicide attempt (Evren et al. 2008). Thus with dissociative disorders carrying such a high risk for suicidal behaviors, it comes as no surprise that they also increase the risk for self-mutilation. Among alcohol dependent patients, those

placed within a dissociative group based on results of Dissociative Experiences Scales were at higher risk for self-mutilation (Evren et al. 2008).

5.16 Traumatized Population

Traumatic events are a common factor in many psychiatric diagnoses including anxiety disorders, such as posttraumatic stress disorder, and personality traits like borderline personality disorder. A history of traumatic experience is quite common among all of the various dissociative disorders as well. Studies have shown a statistically greater incidence of emotional abuse among subsets with dissociative diagnoses than those without such diagnoses (Tamar-Gurol et al. 2008). However, the nature of the trauma can be quite diverse or specific from one dissociative diagnosis to the next. Dissociative fugue states are frequently seen around times of natural disasters, or during wartime among military personnel. Childhood trauma, usually of physical or sexual nature, is seen in 85% to 97% of patients with Dissociative Identity Disorder. Dissociative amnesia is often due to abuse; however, it can be related to wartime experiences as well. Like posttraumatic stress disorder, the severity of symptoms is highly correlated with the intensity of the combat (Kaplan and Sadock, 2007). With the correlation of traumatic experiences and dissociative disorders, presence of one should warrant screening for the other.

5.17 Eating Disordered Population

Many impulsive behaviors have been associated with dissociative disorders, and pathologic eating behaviors are included in this set. In fact, dissociative symptoms are frequently described in individuals with bulimic disorders (Waller et al. 2001). Among the various dissociative diagnoses, it appears that eating disorders are most prevalent with dissociative identity disorder (Kaplan and Sadock, 2007). One study looked at groups of women with eating disorders ranging from anorexia, anorexia with binge-purge subtype, bulimia nervosa, and binge-eating. These women were then administered Dissociative Experiences Scales (DES) to identify those with the most significant dissociative features. Findings showed the binge-purge subtype of anorexia to have the greatest proportion of dissociative cases while binge-eating disorder patients were lower and similar to control groups (Waller et al. 2001). Other factors like abuse or trauma may confound the analysis of studies like these. However, there appears to be a correlation between dissociative disorders and impulsive behaviors, which includes eating disorders.

5.18 Substance Abusing Population

Substance abuse is a common comorbidity with multiple psychiatric disorders including mood, anxiety, and psychotic disorders. Among those with dissociative disorders, substance abuse is frequently reported. However, studies show varied results in regards to their association. One study included inpatients with drug dependence (marijuana, cocaine, heroine, ecstacy, solvents) that often had comorbid alcohol dependence as well. The prevalence of dissociative disorders among the drug dependent inpatients was significantly higher than the general

psychiatric inpatient population, showing correlation between the two (Tamar-Gurol, 2008). Another study included inpatients with alcohol dependence excluding any other comorbid drug abuse. Here the percentage of dissociative disorders among alcohol dependent patients was very similar to the general psychiatric inpatient population. This confers no increased risk of dissociative disorders among alcohol dependent inpatients (Evren et al. 2005). The reason for the difference seen between alcohol versus drug dependence is not known. However, both studies show that dissociative symptoms were present in a majority of the population before alcohol or drug use, 90% and 59.3% respectively (Evren et al. 2005)(Tamar-Gurol, 2008). This emphasizes the importance of screening for dissociative symptoms to potentially help prevent the progression to substance abuse or dependence.

5.19 Pediatric Population

Though pediatric populations are not frequently diagnosed with dissociative disorders, this subgroup may experience the trauma later associated with dissociative diagnoses. One study of drug dependent patients evaluated several variables between groups with dissociative disorders and those without them. Aside from suicide attempts, the only variable to reach statistical significance for increased risk for dissociative diagnoses was emotional abuse taking place during childhood (Tamar-Gurol, 2008). Another study showed that even among children and adolescents treated for dissociative disorders, 82.6% met the criteria for psychiatric disorders at an average of twelve years later. Nearly half of these had diagnosed personality disorders with significantly lower psychosocial adjustment in adulthood (Jans et al. 2008). Thus, recognizing childhood trauma and dissociative symptoms may prove helpful in starting early treatment to help adult adjustment and functioning.

As often is seen in pediatric populations, there are sometimes differences in expression of symptoms between children and adults. In dissociative identity disorder children are noted to be less able to distinguish lapses in time and abnormal behaviors, and often teachers and relatives document these changes. In dissociative fugue adults are often noted to travel large distances or for prolonged periods of time. However, children and adolescents are often much more limited in this capacity and their fugues are often of shorter distances or of shorter duration (Kaplan and Sadock, 2007).

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6 Alcoholism and Psychoactive Substance Use Disorders

Substance use disorders or SUDs encompass a spectrum of conditions varying in severity from problematic use, abuse and varying grades of mild to more severe dependence. Over the last half century, various drug use epidemics have characterised different population groups worldwide. As the knowledge base of clinical neuroscience has expanded, the understanding of these disorders has developed from being viewed as a moral weakness to being viewed as complex biomedical disorders affecting the brain and manifesting clinically as chronic relapsing disorders. In addition, research has demonstrated equivalent rates of relapse for addictive disorders and non-compliance to treatment for medical disorders such as hypertension and diabetes.

6.0.1 Epidemiology

Trends in substance use vary from country to country and fluctuations occur in the prevalence rates across time periods. Epidemiology investigates the distribution and determinants of substance use disorders; as well as patterns of drug use over time and its association with age, gender and associated risk factors. Epidemiologists use various definitions for substance use and substance use disorders. Definitions of substance use can vary from substance use once in past month or year, life time use or use characterised by the fully developed syndrome of addiction. Life time prevalence refers to fulfilling the criteria for a specified pattern of use(i.e., abuse or dependence) at least once in a person's lifetime. Depending on the nature of substance use disorders, the chronicity and the related mortality rates, prevalence and incidence rates can differ markedly. For example, due to the chronic nature of drug dependence, the prevalence rates of substance dependence can be significantly higher than incidence rates. Period prevalence measures, such as past year prevalence, records the rate of patients fulfilling diagnostic criteria over the past year form the total population at risk.

Prevalence:

$$\frac{\text{Total number of cases at time/period}}{\text{Total population at risk at time/period}}$$

Incidence measures refer to the occurrence of newly diagnosed cases over a specified time period. Cumulative incidence or the incidence proportion is usually expressed as the total number of new cases per 10 000 or 100 000 patients over a period of time i.e., over a five year period. Alternatively, incidence rates or density can also be expressed as the number of new cases occurring in the at risk population, over the total number of person years of observation.

Incidence:

Number of new cases over period of time

Total population at risk (without the disease) over period of time

Most large epidemiological samples across countries have found that men are at least 2-3 times more likely than women to use illicit substances and develop substance use disorders such as abuse or dependence (Brady and Randall, 1999). In addition, whereas men start using drugs at a younger age and take longer to develop full blown dependency syndromes; women tend to develop problems with addiction later in life, but develop severe problems more rapidly. However, there is evidence of a trend toward lower differences in substance misuse rates, particularly alcohol abuse, in younger age cohorts; and between males and females in the context of more equal and less traditional gender roles (Grant, 1996; Seedat et al. 2009). Certain religious and ethnic groups also show differential patterns of use. In the UK Afro Caribbean's and in the US black patients are less likely to abuse alcohol and illicit drugs.

In the National Comorbidity Replication Study (NCS-R)(Kessler et al. 2005), conducted between 2001-2003, the lifetime prevalence for alcohol abuse in the general US population was 13.2% and for alcohol dependence 5.4%. Lifetime drug abuse had a lifetime prevalence of 7.9% whereas dependence had a prevalence of 3 %.

Within the United States certain patterns of epidemics in the use of illicit substances have emerged over the past 30 years. Whereas cannabis use peaked in the mid 1970's, there has been a decline in the early to mid 1990's but a rapid upsurge in the mid 1990's. The cocaine use epidemic reached a peak in the early to mid 1980's and has been followed by a stimulant use epidemic dawning in the late early to mid 1990's. Since the start of the new millennium an upsurge in methamphetamine use has plagued many countries among who include the USA, Japan, Australia, South East Asia, Eastern Europe and South Africa.

Epidemiological studies identified different developmental trends in the age of onset of first drug use to the development of dependence. Cocaine dependence follows a risk trajectory of average age of onset of use in early 20's with a comparatively higher cumulative risk of developing dependence than other substances of up to 15-16% in the 10 years following the onset of first use. Whereas the high risk periods for development of dependence for illicit drugs after first use are confined to the late teen years for drugs such as cannabis, early twenties thorough to the early 30's for cocaine, risk of the developing alcohol dependence continues throughout later life (Wagner and Anthony, 2002). Despite stringent drug legislation and law enforcement, substantive evidence that such measures are effective have not been forthcoming

Table 1. Lifetime prevalence of substance use disorders in the general population

Disorder	**Study**	**Lifetime prevalence**
Alcohol abuse	ECA (1980)NCS (1992)NCS-R (2003)	5.8%9.4%13.2%
Alcohol dependence	ECA (1980)NCS (1992)NCS-R (2003)	7.9%14.1%5.4%
Illicit drug abuse	NCS (1992)NCS-R (2003)	4.4%7.9%

Disorder	Study	Lifetime prevalence
Illicit drug dependence	NCS (1992)NCS-R (2003)	7.5%3%

ECA- Epidemiological Catchment Area- study (National Institute on Drug Abuse and Helzer, 1987)

NCS- National Comorbidity Survey (Kessler et al. 1994)

NCS-R- National Comorbidity Survey replication (Kessler et al. 2005)

6.0.2 Pathogenesis

Biological Factors

Neuroanatomy and pathophysiology

The syndrome of drug dependence occurs as a result of a complex interplay of a variety biological mechanisms as well as psychological and social factors. Dependence is characterised by repeated use of a substance resulting that ultimately results in state of neural adaptation in the brain. Various drugs of abuse act on different receptor subsystems with many of these systems converging onto to the final common pathway involved in reward seeking behaviours, the mesolimbic dopamenergic pathway (Kalivas and Volkow, 2005; Koob and Volkow, 2009). Altogether a number of neuro-anatomical circuits are involved in the pathophysiology of addiction. These include:

a) The Reward-Seeking system consisting primarily mesolimbic dopamenergic pathway and its subcomponents. This pathway stretches from the cell bodies of the dopaminergic neurons in the ventral tegmental area of the brainstem (substantia nigra) which project their axons onto the nucleus accumbens in the ventral striatum. Pulsatile stimulation of these dopaminergic neurons result in highly a pleasurable sensations

b) The prefrontal cortex subcomponents are thought to be involved in impulse regulation and modulation of reward seeking behaviour. These components include the OFC orbitofrontal cortex, the DLPFC, and the ventro-medial cortex (VMC) as well as the loop circuits that stretch from the frontal cortex through the striatum to the thalamus and back to the cortex (cortico-striatal-thalamo-cortical circuits or CSTCC). These circuits that traverse the dorsal aspects of the striatum are also implicated in the compulsive aspects of drug addiction.

c) The extended amygdala (consisting of the central nucleus of the amygdala, the Bed Nuleus of the striae terminalis and the shell of the nAcc) and its connections with the VTA and Nu Accumbens, plays an important role in learning and conditioning of behaviours related to drug use.. The extended amygdala is sensitive to stress hormones such as cortisol, and plays a potentially important role in the triggering of relapses into drug taking behaviour caused by environmental and intrapsychic stressors.

d) The basolateral cortical amygdala. This structure represents the neocortical cellular layers of the amygdala and is thought to play an important role in environmental cue detection.

This structure is therefore potentially important in cue induced drug taking behaviours. People, places and objects such as drug paraphranelia that has become conditioned with drug taking can potentially lead to stimulation this anatomical area to induce relapses.

e) Memory systems in the hippocampal formation, involved in the memory consolidation of events associated with substance use. This system is interconnected among others with the extended amygdala.

Pathophysiology: Substance binge/intoxication phase and type 1 craving (Stage I addiction)

The initial use of substances, in particular psychostimulants such as cocaine and methamphetamine, is associated with a surge in dopamine release in the mesolimbic dopaminergic pathway. The principal neurotransmitter in the reward pathway is dopamine which binds to D1 and D2 receptors. Whereas drug like cocaine and amphetamines result in a direct surge of dopamine release at dopaminergic synapses (via Dopamine re-uptake-DRI- inhibition in case of cocaine and increased release in case of amphetamines) other substances such as opoids and alcohol and cannabis are thought to indirectly result in increased dopamine release after affecting brain stem mu opoid, GABA inhibitory interneurions and CB1 (cannabinoid type one) receptors. In addition to the effects mediated indirectly via the dopaminargic system on learning, conditioning and reward-motivation, non stimulant drugs such opiates, cannabis and alcohol also exert effects on the glutamatergic, serotonergic, and cannabinoid systems that have been postulated to be crticial in the pathophysiology of addictive syndromes, independent of the effects of the dopaminergic system. The basolateral and extended amygadala is associated with craving, also known as type I craving, characterised by operant conditioning in the form of positive reinforcement of drug taking behaviour paired with rewarding sensations as well as classical conditioning by the pairing of neutral stimuli with the drug of abuse.

Pathophysiology: Withdrawal and protracted withdrawal/type 2 craving (Stage II addiction)

Prolonged use of a substance results in a state of neuroadaptation. Human Imaging studies have revealed decreased dopamine uptake activity in frontal striatal areas associated with chronic drug use. This downregulation of dopaminergic function results in a dampened reward system and the clinical phenomenon of tolerance. In addition repeated use and binging activates the hypothalamic pituitary axis (HPA axis) driven stress response and hormones such as corticotrophin releasing hormone (CRF) are mobilized. Anti stress hormones such as neuropeptide Y (NPY) levels also decrease. The activation of the stress response is has also been conceptualized as an anti-reward system. Whereas the presence of the substance is experienced as pleasurable the withdrawal is experienced as unpleasant and anhedonia frequently characterises protracted withdrawal states. In contrast to the positive emotional state of intoxication, withdrawal is associated with a negative emotional state. These negative emotional states are thought to drive increased drug taking. Increased drug use associated with stress/negative emotional states is termed type 2 craving or negative reinforcement (Koob, 2009).

Pathophysiology: Relapsing recurring stage (Stage III addiction)

In addition to neuro-adaptation at transmitter and receptor level, intracellular molecular changes also occur during the state of drug dependence. These include the activation of transcription factors such as CREB (cAMP response element binding protein) and delta Fosb. These transcription factors in turn lead to the switching on of genes that code for neurotransmitter receptors, enzymes involved in the synthesis of neurotransmitters and to altered neurotransmitter receptor numbers (up or down regulation). Increased cAMP in the nucleus accumbens associated with opoid, cocaine and alcohol use has also been linked to increased expression of the kappa opioid receptor that bind to the dysphoria inducing hormone dynorphine. This mechanism is thought to underlie the development of tolerance and is associated with the negative emotional state characterising withdrawal of the substance of abuse (Hyman, 2005). These molecular changes establish addiction and drive the relapsing and recurrent nature of addition.

Pathophysiology: Genetic vulnerability

Research into the genetics of alcohol dependence based on family, twin, and adoption studies have revealed that the heritability of alcohol dependence can be as high as 60%-80%. Genome wide association studies have implicated a number of genes in the development of alcoholism. In particular genes involved in the metabolism of alcohol are thought to play an important role. Asian populations are known to have low rates of alcoholism in comparison to Europeans. Persons from Asian descent experience highly unpleasant reactions upon alcohol ingestion such as severe nausea, flushing and tachycardia. This reaction is due to a rapid accumulation of the toxic breakdown and accumulation of the alcohol metabolite, acetaldehyde. This clinical observation lead to a search for associations with enzymes such as alcohol dehydrogenase (ADH) that converts alcohol into acetaldehyde and acetaldeyhe dehydrogenase which converts acetaldehyde to acetate. This search has revealed that variants in the alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) genes on chromosomes 4q and 12q respectively, are implicated. A variant of the ADH gene, ADH1B on chromosome 4q that encodes for a more robust ADH enzyme leading to higher levels of the toxic metabolite acetaldehyde, has been shown to protect against alcoholism in a Chinese population, reducing the rate of alcoholism with up to 80%. In turn a variant of the ALDH2 gene on chromosome 12q that produces weaker acetaldehyde dehydrogenase enzymes have been shown to reduce alcoholism with up to 67% in heterozygous subjects. As alcohol is an agonist on GABAA receptors, a search for genes encoding for the GABA receptor has revealed a strong relationship between alcoholism and the GABRA2 subunit gene on chromosome 4p that encodes for the ?2 subunit of the GABAA receptor. The GABAA receptor plays an important role in mediating the effects of alcohol intoxication as well as withdrawal (Hartz and Bierut, 2010).

Nicotine dependence carries a heritability estimated as high as 75%. Strong associations have been found between nicotine dependence and variants of genes coding for nicotinic cholinergic receptors (nAChR's). In particular the gene CHRNA5, coding for the ?5 subunit of the nicotinic cholinergic receptor has been implicated. This gene is located on chromosome 15q. Nicotinic cholinergic receptors are distributed in the striatum on dopaminergic neurons and

interact with these neurons in the dopaminergic reward pathways. In turn the CHRNA5 gene has also been implicated in cocaine dependence (Hartz and Bierut, 2010). Of recent interest has been the study of potential gene environment (GxE) interactions in the development of addictive disorders. Whereas many of these findings represent non specific risk factors for a variety of psychiatric disorders, they are also likely to play a role in addictive disorders. Gene environment interaction studies have demonstrated interactions between variants of genes such as the serotonin transporter gene (5-HTTLPR) short and long variants and childhood maltreatment and negative family relations; the monoamine oxidase (MAOA-LPR) gene and childhood maltreatment and sexual abuse, as well as the GABRA2 gene and marital status. Although the findings of GXE studies are intriguing, many of these studies await replication(van der Zwaluw and Engels, 2009).

Psychological Factors

Learning, conditioning and cognitive factors

The development of drug dependence is driven by two different types of associative learning behavioural psychologists refer to as classical and operant conditioning.

Classical (or Pavlovian conditioning-referring to Pavlov's experiments with dogs) consists of the repeated pairing of a neutral stimulus with a particular stimulus (uncontioned stimulus) that elicits a physiological, reflexive response (unconditioned response) such as activation of salivary glands or activation of a sexual response. With repeated co-administration of the unconditioned stimulus with the neutral or conditioned stimulus the neutral stimulus becomes a conditioned stimulus (CS) and elicits a conditioned response (CR). People, places and objects associated with the drug use can become conditioned to elicit conditioned responses such as craving before using and therefore reactivate substance seeking behaviour.

Operant conditioning refers to a positive or negative reward that follows certain behaviour such as taking a drug. Thus the euphoriant effects of a drug will positively reinforce drug taking behaviour. Negative affective states associated with the absence of drug taking behaviour or withdrawal become a negative reinforce that also increase further substance use behaviours.

In addition to behavioural factors, cognitive styles of persons with addictions can also perpetuate addictive behaviours. Dysfunctional and irrational beliefs about drug taking, triggered by environmental cues or intrapsychic stressors, can also lead to craving and consequent relapses into drug taking cycles. These beliefs may include thoughts such as "I cannot socialize without drinking," "I need some drugs to enjoy myself," "I am able to control my drinking," "there is no life for me without drugs, as I am essentially a bad person."

Cycle of change and motivation

Prochaska and Diclemente have forwarded the cycle of change model of addiction (DiClemente et al. 2004). This model forms a useful framework of understanding motivation to change and forms the basis for motivational enhancement therapy. According to this model patients

cycle through a number of stages throughout a recovery process. Patients can enter or exit at any stage of this cycle. These stages are:

a) Precontemplation stage: a stage where drugs are not considered problematic and dependence on the substance is denied.

b) Contemplation stage: Ambivalence is developed where the negative impacts of substances are weighed up against the perceived benefits, and change is contemplated.

c) Preparation: During this phase the person devises a plan for implementing change and strengthens their motivation to commit to such a plan c) Determination: The client is determined to seek help

d) Action: Advice is followed and a rehabilitation plan is followed

e) Maintenance phase: triggers for use are identified and new coping strategies are learnt, leading to a new lifestyle.

f) Relapse: Relapse into substance taking behaviour are viewed not in a negative light but as positive learning experiences for the future. Clients can cycle back and forth through these stages and recycle through these stages until a level of completion is reached that allows for a sustained change. Researchers also differentiate between readiness for change and readiness to engage in treatment. Whereas a client may show behaviours indicating a readiness to change, this does not necessarily translate into a willingness to follow a specific treatment program. Self-efficacy, the degree of confidence a client has in their ability to effect changes, plays an important role in shaping motivation and low self-efficacy can be an important predictor of relapse.

Understanding the psychodynamics of addiction

Although unmodified psychodynamic techniques play a limited direct role the treatment of most persons with addictions, psychodynamic theory is useful in understanding the behaviour and family interactions that characterise the lives of people with addiction. Psychodynamic understanding is also useful in informing other therapeutic modalities such as CBT, MET, and group therapy. Comorbidity with various personality disorders is common in patients with addictions, with as many as 73% of addicts receiving a diagnosis of a co-occuring personality disorder, a prevalence rate several times that in psychiatric patients or persons without any psychiatric disorder. The most common personality disorders are borderline and antisocial personality disorders with the later particularly prevalent in individuals with alcohol use disorders (Verheul, 2001).

The self medication hypothesis advanced by Khantzian has been put forward to explain substance taking behaviour (Khantzian, 1997). According to these theory patient abuse substances to aid in the regulation of strong affects and painful emotions that the person may experience as overwhelming. Furthermore the good, euphoriant effects of substances are used as a substitute for deficient positive affirmation of the self by significant others in the person's past, leading to low self esteem and deficits in self care.

During the early stages of precontemplation and contemplation where substance dependence may not be considered problematic by the client, primitive ego defences characterise the defen-

sive style of the individual. These defences include denial of the addiction, splitting objects, family members and loved ones into all good or bad and projective identification whereby family members often unconsciously identify with distressing internal self-representations that have been projected onto others by the client and therefore either become the good, "benevolent rescuer" or the "punitive, bad family member."

A subjective sense of overwhelming powerlessness characterises persons with addictions. Together with the roles of benevolent rescuer and malevolent punisher, feelings of helplessness are often projected onto family members who unconsciously identify with this sense of loss of control and power and may defensively insist on unhelpful, inappropriately restrictive and even punitive measures. Important distinction therefore need to be made between setting limits (a desirable therapeutic measure) and punishment (undesirable and may worsen the addiction) as well as rescuing behaviour which will take away the effects of the substance use on the lies of the addicted individual and absolve them of responsibility and therefore further enable substance taking behaviour. In addition to more primitive defences, more mature, neurotic defences such as rationalization and intellectualization also characterise certain individuals with addictive disorders. With substance use disorders, particularly higher are functioning personalities with more mature and neurotic defensive personality structures.

6.0.3 Phenomenology

Symptoms and classification

The term addiction is not formally endorsed by the DSM-IV-TR or ICD-10 diagnostic classifications. A proposed revision to the DSM-IV-TR is that this term be reintroduced to differentiate benign dependence states on medication such as antidepressants and beta blockers from malignant and dysfunctional states that characterise drug and alcohol dependence. The term "addiction" is sometimes used interchangeably with the category described in diagnostic systems as substance dependence. The syndrome of substance dependence or addiction develops over time with repeated use of the substance and is accompanied by neuro-adaptive changes in the brain. The diagnosis of a substance use disorder is made clinically through patient and collateral interview and is based on a clustering together of various symptoms. The most used diagnostic systems used to diagnose addiction are the DSM-IV (American Psychiatric Association, 2005) and the ICD-10 (World Health Organization Geneva, 1992). See table X for the ICD-10 diagnostic criteria. These systems of disease classification sets out specified operational criteria that need to be present before a diagnosis can be made of drug abuse or dependence. Laboratory tests for substance use disorders can be used as confirmatory tool where the reliability of self report or collateral sources of information is questionable.

Substance abuse (as it is referred to in the DSM-IV) or harmful use (as referred to in the ICD-10) consists of the presence of behaviour whilst under the influence of the effects of a substance that result in adverse social, psychological, legal or physical consequences to the person involved. (See table 2 for ICD-10 Diagnostic Research Criteria) The ICD-10 differs from the DSM-IV in that abuse is termed "harmful use" and the criteria is less specific than the DSM-IV and requires symptoms to be present for at least one month or repeatedly within a twelve month period. The DSM-IV-TR specifies certain criteria to be present relating to failure to fulfil social and occupational responsibilities, using substances in circumstances

that are physically hazardous such as driving under the influence, negative consequences in interpersonal relationships and being frequently in trouble with the law as a result of substance use.

Table 2. DSM-IV and equivalent ICD-10 substance use disorders

ICD-10	DSM-IV-TR
"Substance use disorders"Harmful useSubstance dependence syndrome	"Disorders due to psychoactive substance abuse"Substance abuseSubstance dependence

Substance dependence is a syndrome that is characterised by compulsive use of the substance and loss of control over substance using behaviour. It can be accompanied by the phenomenon of tolerance to the effects of the substance and substance specific withdrawal syndrome. Tolerance is characterised by the need for increased amounts of the substance to achieve the same desired effect or by the same dose not resulting in the desired effects. Withdrawal is characterised by a characteristic cluster of symptoms on cessation or reduction of the substance. If either tolerance or withdrawal is present ICD-10 and DSM-IV allow the subtype specification of physiological or physical dependence to be noted. Substance dependent individuals also spent increasing durations of time engaging in substance taking behaviour and may give up other activities previously enjoyed in order to use the substance. Substance use continues compulsively despite adverse consequences to the person's psychological or physical health.

Table 3 sets out the key similarities and differences in ICD-10 and DSM-IV diagnostic criteria for substance dependence.

As noted the term "addiction" is often used interchangeably with substance dependence. Addiction can be defined as a chronic relapsing medical disorder characterised by

a) loss of control over substance intake

b) and compulsive drug use associated

c) with the development of neuro-adaptations that result in the presence of

d) negative affective states when the substance is withdrawn.

Table 3. ICD-10 criteria for harmful use and dependence

Harmful use: Mental or physical harm that may be associated with impaired judgement clearly caused by use of a substance within a 12 month period.A) There must be clear evidence that the substance use was responsible for (or substantially contributed to) physical or psychological harm, including impaired judgement or dysfunctional behaviour.B) The nature of the harm should be clearly identifiable (and specified).C) The pattern of use has persisted for at least 1 month or has occurred repeatedly within a 12-month period.D) The disorder does not meet criteria for any other mental or behavioural disorder related to the same drug in the same time period (except for acute intoxication).

Dependence syndrome: Three or more of the following manifestations should have occurred together for at least one month or, if persisting for periods of less than 1 month, should have occurred repeatedly within a 12 month period:1) A strong desire or sense of compulsion to take the substance.2) Impaired capacity to control substance taking behaviour in terms of its onset, termination, or levels of use, as evidenced by the substance being often taken in larger amount s over a longer period than intended, or by a persistent desire or unsuccessful efforts to reduce or control substance use.3) A physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance or by use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms.4) Evidence of tolerance to the effects of the substance, such as that there is a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance.5) Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time spent in activities necessary to obtain, take or recover from the effects of the substance.6) Persistent use of substance despite clear evidence of harmful consequences, as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm.

Table 4. Differences and similarities between ICD-10 and DSM-IV criteria for substance abuse and dependence

ICD-10	DSM-IV-TR
Harmful use: Psychological or physical harm that may be associated with impaired judgement clearly caused by use of a substance within a 12 month period.	**Abuse:** Defined operational criteria of which at least one out of 4 must be present within a 12 month period. Criteria refer to continued use despite harmful interpersonal consequences, failure to fulfil major social and occupational roles, using substances in hazardous circumstances and legal consequences such as arrests for behaving under the influence of substances.
Dependence syndrome1. At least 3 symptom criteria have to be present concurrently for at least 1 month or repeatedly present if less than one month within a 12 month period.2. Includes the concept of desire and craving with compulsive use.3. Further criteria in ICD-10 and DSM-IV overlap with difference in which criteria are independent or present as the same construct.	**Dependence**1. Also specifies that at least 3 symptom criteria have to be present in a 12 month period from an operational set but not necessarily concurrently.2. Does not refer to desire or compulsion to use (craving).3. These are essentially the same with the exception that certain criteria treated independently rather than as one construct.

Substance intoxication syndromes:

Syndromes of intoxication that are specific to the substance of abuse characterise use of each substance. Intoxication is usually defined as a substance specific syndrome that develops during or immediately after the ingestion of a substance and is characterised by maladaptive behavioural or psychological changes as a result of the effect of the substance on the central nervous system. Drugs of abuse can broadly be classified into "uppers" and "downers" and often persons addicted to drugs of abuse use a combination of both stimulant and depressant substances. Classified within the "downer" group are substances such as alcohol, cannabis, heroin and sedative hypnotics. Uppers consist of stimulants such as amphetamines, methamphetamines, and cocaine and club drugs such as ecstasy. A third designated class of substances include the hallucinogens and consist of substances such as LSD, mescaline and psylopsiben. The specific features of each syndrome is determined by the unique effects of each substance on the receptor systems of the brain as well as the half life of the substance which determines the duration of the substance related effects.

Table 5 contains the details of various substance intoxication syndromes.

Table 5. Substance intoxication syndromes

Substance of abuse	**Behavorial, psychological and physical effects**	**Half life and onset and duration of effects**	**Principle receptor and neural systems affected**
Alcohol	Disinhibition, impaired judgement, argumentativeness, aggression, lability of mood. Higher doses can lead to sedation, incoordination, slurred speech, flushed face and stuperous states.	Follows zero order kinetics with catabolic enzymes reaching saturation at certain levels and blood levels increasing exponentially. Effects more pronounced when blood levels are rising compared to when they are falling.	Allosteric modulator of GABAA receptors. Impacts on neural membrane integrity. Acts on opioid and dopamine systems.

Substance of abuse	**Behavorial, psychological and physical effects**	**Half life and onset and duration of effects**	**Principle receptor and neural systems affected**
Cannabis	Euphoria, disinhibition, anxiety, agitation, increased appetite, incoordination, mild euphoria, ,asedation, derealisation, depersonalization, temporal slowing (time passes slower) conjunctival injection.	Onset reaches peak 10 minutes after ingestion and declines after 1 hour. Due to uptake into fatty tissue effects can potentially be prolonged. Can be detected in urine for up to 4 weeks in heavy, chronic users.	Cannabinoid receptors (CB1, CB2), dopamine receptors
Amphetamines	Euphoria, elation, inflated self esteem, grandiosity, decreased appetite, abusiveness and aggression, argumentativeness, repetitive stereotypical movements, paranoid ideation, hallucinations with intact sensorium, tachycardia, dilated pupils, hypertension, cardiac arrhythmias.	"Rush" or high often more intense than other stimulants and can last from 8-12 hours. Half life up to 20 hours for methamphetamine.	Dopamine presynaptic neurons, Vesicular monoamine transporter (VMAT2), dopamine transporter (DAT) and receptors

Substance of abuse	**Behavorial, psychological and physical effects**	**Half life and onset and duration of effects**	**Principle receptor and neural systems affected**
Cocaine	Euphoria, increased energy, inflated self esteem, grandiosity, hallucinations usually with intact sensorium, hypervigilance, decreased appetite, abusiveness and aggression, argumentativeness, repetitive stereotypical behaviours, paranoid ideation, tachycardia, dilated pupils, hypertension, cardiac arrhythmias, weight loss.	"Rush" or high lasts few minutes after intake. Half life ranges from 30 to 90 minutes.	Dopamine transporter (DAT) and receptors
Heroin	Brief euphoric rush followed by apathy and sedation, psychomotor retardation, impaired attention and judgement, interference with personal functioning, pupillary constriction drowsiness.	Euphoric sensation lasts a few minutes only. Effects wear off in 4 hours with withdrawal symptoms and signs starting after 8 to 12 hours.	Mu (μ) opioid receptors, ?opioid receptors, dopamine neurons indirectly

Substance of abuse	Behavorial, psychological and physical effects	Half life and onset and duration of effects	Principle receptor and neural systems affected
Hallucinogens (LSD, mescaline)	Anxiety, visual, auditory or tactile hallucinations whilst awake and alert, depersonalization, derealisation, ideas of reference, paranoid ideation, lability of mood, impulsive acts, tachycardia, blurring of vision, palpitations, inco-ordination	Effects subside after 6 to 12 hours.	Serotonergic and dopamineric neural systems
Substituted amphetamines (MDMA, "ecstasy")	Combination of stimulant and hallucinogen effects: mood elevation, increased self confidence, sensory sensitivity, peaceful feelings coupled with insight, empathy and closeness to other people.	Effects last 4 to 8 hours.	Serotonergic and dopaminergic neural systems.

Substance withdrawal syndromes

Alcohol withdrawal

Depending on the severity of the dependency syndrome alcohol withdrawal can range from mild and spontaneously resolving states to severe, potentially life threatening states. Mild withdrawal is characterised by gastrointestinal symptoms such as nausea, retching and vomiting, sympathetic hyperactivity as manifested by sweatiness, tachycardia, tremor and insomnia. In the majority of cases mild to moderate withdrawal states can be managed with outpatient detoxification regimes. Less than 5-10% of patients with alcohol dependence will develop complicated withdrawal also termed delirium tremens. Risk factors for complicated withdrawal include:

a) Previous history of complicated withdrawal b) History of withdrawal seizures c) Severe nutritional deficiencies (Vit B and thiamine) d) Underlying medical complications such as pancreatitis, liver damage, peptic ulceration or oesophageal varices.

Delirium tremens typically develops 48 to 72 hours following cessation of drinking and is characterised by clouding of consciousness, severe tremor, visual and tactile hallucinations

often in the form of small animal figures or insects, agitation and fidgetiness as well as nausea and vomiting. Withdrawal seizures can also develop 48 to 72 hours following the last drink. Delirium tremens is considered a medical emergency and treatment in a facility geared towards the management of medical ill patients is essential.

Wernicke's encephalopathy is a further potential complication of alcohol withdrawal. This condition can arise due to nutritional depletion of thiamine leading to a cluster of neurological symptoms on the background of a delirium. Physical signs of Wernicke's encephalopathy include opthalmoplegia with cranial nerve III and VI palsies as well as ataxia. Only 10% of patients with Wernicke's will have the classical triad of confusion, ataxia, and nystagmus. Cranial nerve signs also only occur in about 25% of patients. Therefore, a diagnosis of Wernicke's should always be considered in patients' who present with alterations in level of consciousness in the context of alcohol withdrawal. Untreated Wernicke's can result in death in up to 20%, and as many as 20% of patients go on to develop neuronal damage in the diencaephalic brain regions such as the mediodorsal thalamus, periaquadauctal grey and mammilary bodies of the hypothalamus. Damage in these neuroanatomical regions can result in anterograde amnesia, characterised by the inability to learn new information. Also known as diencephalic amnesia, this form of memory loss is characteristic of Korsakoff's psychosis, which is diagnosed according to the DSM-IV as "Alcohol induced persistent amnestic disorder."

Opioid withdrawal

Discontinuation of heroin and other opioid derivatives is characterised by a pronounced withdrawal syndrome. Although highly unpleasant, unlike alcohol withdrawal heroin withdrawal is rarely associated with life threatening complications. The syndrome of withdrawal is characterised by severe dysphoria, craving for heroin, agitation, yawning, diaphoresis, lacrimation, piloerection (goose bumps) pupil dilatation, muscle and abdominal cramps as well as diarrhoea. For drugs such as heroin with a short duration of action, the acute withdrawal syndrome usually reaches a peak after 48 to 72 hours and subsides after 7 to 10 days.

Stimulant withdrawal (cocaine and methamphetamine)

Characteristic withdrawal syndromes have been described for stimulants such as cocaine, amphetamines and methamphetamine. The acute withdrawal syndrome usually has its onset within 12 to 24 hours of the last dose. The acute withdrawal syndrome is sometimes described as a "crash" after the period of a high. This syndrome is characterised by feelings of intense sadness and depression, severe fatigue and a tendency to oversleep and eat. The acute withdrawal syndrome typically subsides after 10 to 14 days. This is followed by a period from week 2 to week 8 post cessation that is characterised by renewed energy and a newfound confidence in abstinence. This period has also been described as the "honeymoon period" where persons typically feel confident that they are able to quit using stimulants on their own. In the treatment setting this can often be characterised by treatment drop-outs. By 2 months post drug cessation a third phase sometimes described as "the wall" is described. This phase is characterised by severe fatigue and a loss of the ability to experience pleasure (anhedonia). Usual routes to experience pleasure are often drug associated. Recovering addicts often experiences this stage is profoundly isolating.

Comorbidity

Rates of substance use disorder have been reported as high as 75% in the treatment settings for patients with severe mental illness such as schizophrenia. The odds ratio for bipolar mood disorder in patients with substance use disorders in the NCS study has been reported to be as high as 6.8. Similarly major depressive disorder occurs in up to half of treatment seeking individuals with substance use disorders whereas the rates of substance use disorders in persons diagnosed with major depression is 2-3 times that of the general population (Kessler et al. 1996). Patients with anxiety disorders in particular panic disorder OCD and PTSD are also more likely to have a co-occurring substance or alcohol use disorder than persons from the general population. Whereas women with alcohol dependence are more likely to have co-occurring anxiety and mood disorders as compared to men, men are in turn more likely to have co-morbid ADHD, conduct disorder and antisocial personality disorder (Brady and Randall, 1999).

Clinical assessment

Substance use history and mental status examination:

In the routine clinical setting a thorough substance history should include the following:

a) The various different substances used including the substance of preference.

b) Age at first use, the frequency and amount of use over time.

c) Date of last use.

d) The amount of money spent on substances.

e) The amount of time spent daily on drug taking.

f) Attempts at trying to quit, as well as the duration of abstinent periods.

g) History of medical/physical complications including overdoses. This includes a history of risk taking behaviour placing the individual at risk of contracting transmissible conditions such as HIV or Hepatitis B.

h) An assessment of the social and relationship consequences of the substance.

i) Screening for mood, anxiety, psychotic and other psychological symptoms that may co-occur with drug use.

j) Family history of drug dependence and abuse.

k) A thorough forensic history and history of any legal involvement.

l) A detailed personal history and quality of relationship with important attachment figures as well as important developmental tasks.

Diagnostic and screening instruments:

The Alcohol Use Disorders Identification Test or AUDIT (Saunders et al. 1993) is a brief (2-3 minute) 10-item screening tool of particular use in primary care, general practice settings.

It includes both a self report and clinician administered version that rate items relating to different aspects of drinking patterns, harmful use and dependency on a 4-point Likert-type scale ("never" to "daily or almost daily"). A total score of more than 8 on this scale is indicative of alcohol related problems that calls for further in-depth diagnostic interviewing. Lower cut-off scores than 8 are suggested for female populations. This instrument has demonstrated good sensitivities varying from 0.76 to 0.92 and specificities from 0.70 to 0.92 in various populations including psychiatric patients with severe mental illness and primary are patients (Reinert and Allen, 2002).

The Michigan Alcoholism Screening Test (MAST)(Selzer, 1971) is a slightly more comprehensive instrument that in addition to current alcohol use also assesses use over the subject's entire lifetime. This self report screening instrument consists of 25 yes or no items and is available in two shorter 13 and 10 item versions. It is suitable for a variety of clinical and non-clinical settings. In addition to assessing alcohol use it also enquires about a number of related consequences of alcohol abuse such as medical, psychological, psychiatric, social, interpersonal, and occupational complications (Selzer, 2008). Despite its strength as regards comprehensiveness it is less likely to be suitable in busy time pressured clinical settings.

The Drug Abuse Screening Test (DAST)(Skinner, 1982) is a self report instrument based on the MAST but specific to illicit drug use. Similar to the MAST it assesses the presence of a variety of social, occupational, interpersonal and medical consequences relating to illicit non-medical drug use. Depending on the cut-off scores, the 20, 28 and 10- item versions of the DAST have a high sensitivity and specificity values for the detection of DSM-III-R diagnoses of substance use disorders diagnoses across a variety of settings including in patients with severe mental illness. This instrument is suitable for patients who are non-treatment seeking and assesses overall consequences of all, including polydrug use and does not specify which drugs are more likely to cause particular consequences. The test requires less than 10 minutes completing and scoring.

A brief and clinically useful tool to identify alcohol related disorders is the CAGE questionnaire (Ewing, 1984). This very brief instrument takes less than 1 minute to complete and consists of 4 brief questions as contained in the acronym "CAGE." Cut down- refers to the need to cut down or decrease drinking; Annoyed refers to feeling annoyed at criticism from others about drinking too much; Guilt refers to feeling bad or guilty about drinking; Eye opener refers to the need to have a drink first thing in the morning. The total score of the test is out of 4. A cut-off of 1 out of 4 has a high sensitivity varying from 0.86 to 0,90 but lower specificity (and hence higher false positive rate) ranging from as low as 0.52 to 0.53 to detect alcohol use disorders of clinical threshold (abuse and dependence as identified by DSM or ICD-10 criteria). Consequently some have recommended that a cut-off of ?2/4 be used to identify abuse or dependence as a result of the higher specificity and hence lower false positive rates. Clinicians also need to be aware of its limitations in certain populations as studies have shown to be a less accurate instrument in white women, pregnant women and college students who tend to binge drink (Dhalla and Kopec, 2007).

A similar test to the CAGE is the TWEAK test (Russell et al. 1991). This brief 5-item self or clinician rated instrument has been designed for and specifically validated in samples of females including pregnant women. The name of the scale is an acronym derived from the letters that represent the main constructs that are measured. In the TWEAK-HOLD version designed for the binge drinking population Tolerance refers to the amount of drinks a person can hold. In the TWEAK-HIGH version the question is phrased "does it take three

or more drinks to feel high?" Worried refers to complaints or worries expressed by friends or close relatives about the patients drinking in the past year. Eye-openers refer to having a drink first thing in the morning. Amnesia refers to reports from others of blackouts where events or conversations are forgotten while drinking. The K refers to cut down or the need to cut down on drinking. The first two items are allocated a score of 2 if rate positive and the remaining items are all scored one to give a total for the entire test of 7 points. Cut–off scores of 2 or higher have been demonstrated to be associated with harmful drinking in pregnancy complicated by significantly lower birth weight, head circumference, APGAR scores and cognitive deficits by age 6 years. Cut-offs of 3 or higher are characterised by good levels of sensitivity and specificity to detect alcohol dependence in women in general population and emergency room settings (Russell et al. 2008). The TWEAK performs less well in primary care settings to detect harmful drinking where the AUDIT may be a more valid test (Bush et al. 2003).

In addition to non-structured clinical diagnostic classification systems such as the ICD-10 and DSM-IV, more structured instruments exist to aid in the diagnosis of substance abuse and dependence. The Structured Clinical Interview for DSM-IV or SCID-I (First et al. 1994) is a semi-structured clinical interview designed to generate categorical diagnoses based on DSM-IV diagnostic criteria. This interview is available in a clinician and research version and takes on average 90-120 minutes to complete depending on patient factors and clinician experience. Formal training is required and experience and background in clinical work is advantageous although not essential to conduct this interview successfully. The instrument consist of several modules that assess various mental disorders in addition to substance use disorders and depending on the needs and research designs or clinical need these modules included or excluded with the module assessing substance use disorders.

The Mini International Neuropsychiatric Interview (MINI)(Sheehan et al. 1998) is a briefer diagnostic instrument in comparison to the SCID-I and that generates a wide variety of diagnoses including substance and alcohol use disorder categories. The MINI is available in variety of languages including English and takes approximately 15 to 20 minutes to complete. Three versions the MINI, MINI-plus and MINI kid are available. The MINI evaluates the presence of 17 axis I disorders, with 8 additional disorders included in the MINI plus. The interviewers are required to have some training in its administration (2-3 hour training) with non clinicians requiring more extensive training. The MINI questions are structured to be delivered verbatim and have a yes no outcome. This instrument has been designed to maximise sensitivity introducing the possibility of false positives and therefore necessitating more in depth probing by clinicians in cases where positive predictive values need to be maximized (the likelihood that a positive screen represents a true positive). The most widely used scale in the measurement of addiction severity within addiction treatment settings is the addiction severity index or ASI (McLellan et al. 1992). This multidimensional instrument measures the consequences of drug use across 7 domains. These domains include the assessment of drug and alcohol use, medical consequences, psychiatric complications, impacts on employment and support, family history, family and social support and legal status. This scale requires training in its administration and takes 40-60 minutes to complete. Severity can be calculated by calculating composite scores and by means of clinician rated severity scale for each measured domain. It can be used to track treatment progress over time. Its limitations include low test retest reliability in some populations such as in dual disorder, severely mentally ill and homeless individuals, and lower inter-rater reliabilities among interviewers with less training. The calculation of composite scores has been recommended

in follow up studies as opposed clinician rated severity scales (McLellan et al. 2008; Makela, 2004).

Laboratory tests:

In the clinical setting it is important to realize that laboratory tests merely detect recent use of substances and are not diagnostic of abuse, dependence or addiction. During the diagnostic work-up laboratory tests should only be used when the reliability of the patient's account of use is in doubt. In turn routine random, unannounced testing does from an important part in treatment settings, where rewards or limit setting may be contingent upon urine test results.

Laboratory tests are routinely based on urine samples but hair, blood, saliva and sweat samples can also be used. The availability of inexpensive on-site, point of collection rapid urine drug tests has made routine testing much more practically useful to many treatment facilities. Urine immune-essay tests typically a have shorter detection range, varying from 1-3 days with all the typical drugs of abuse usually eliminated from the body within 48 hours. One exception is in chronic heavy users of cannabis where detection in the urine can be present for up to 1 month. Hair analysis by means of gas chromatography, mass spectrometry (GCMS) has a much wider detection range vary from 7-90+ days. Hair analysis, although prone to false positives in cases of passive ingestion of substances, can also quantify severity of drug use as the length of hair containing drugs of abuse correlates with frequency of use. In addition hair testing may be useful in opiate addicts in patients claiming false positive urine test due to poppy seeds, or in patients who are cheating or evading urine drug testing (Dolan et al. 2004).

Blood tests are also useful in the treatment of patients with alcohol dependence. The most sensitive and specific tests are serum gamma glutamyl transferase (GGT) and carbohydrate deficient transferrin (CDT). Although the most sensitive of markers, GGT is also influenced by age and obesity and can be false positive as a result of a number of chronic illnesses such as liver disease and medication treatments .CDT, although less reliable in female patients, is specific to high levels of alcohol intake and when done in combination with GGT increases sensitivity and specificity. These markers will remain positive for up to 2-3 weeks following cessation of alcohol use. Mean corpuscular volume of red blood cells (MCV) is another sensitive marker, particularly in female patients and remains positive for up to 2-4 months following the start of abstinence (Niemela, 2007).

6.0.4 Treatment

Treatment setting and level of care

The consequences of addictive disorders span across a wide array of potential biopsychosocial complications. Consequently the treatment needs of individuals with addictions span across medical, psychiatric, psychological, legal, social occupational and financial domains. Due to this multidimensional nature of treatment needs many health providers are likely to be involved in the treatment process. Treatment providers can include medical services, specialized psychiatric services, social services, the criminal justice system and psychological services. As the treatment needs of patients are highly heterogeneous, treatment intensity and treatment modalities needs to be matched to the individual patients needs. This requires

frequent and effective interaction between various role players in the addiction treatment process. A standardized intake assessment procedure that determines the level and intensity of the required treatment needed is essential to ensure integrated and appropriate treatments. Research has demonstrated that patients who are not appropriately matched in terms of the intensity of treatment are more likely to drop out of treatment and relapse earlier (Deck et al. 2003). One such standardized assessment procedure is the revised version of Patient Placement Criteria (PPC-2R) for the treatment of substance related conditions endorsed by the American Society of Addiction Medicine (ASAM)(Mee-Lee et al. 2001). This system allows for placement in five main levels of care with further specifications in the revised system. These levels consist of an early intervention level (level 0.5), outpatient based care (level I), intensive outpatient or partial hospitalization care (level II), inpatients residential care (level III) and medically managed inpatients services (level IV). In addition the type of care is further determined along six dimensions: acute intoxication or withdrawal potential; biomedical conditions or complications; emotional, behavioural or cognitive conditions and complications; readiness to change; relapse, continued use or continued problem potential and recovery environment.

Stages of treatment

Treatment can be conceptualized in phases according to the stage of readiness of a client. However, these stages should not be regarded as rigid as therapeutic interventions may be applicable across different stages of motivation. Both psychological and pharmacological interventions differ across the various stages of change.

a) Precontemplative, contemplative and early determination stages:

Psychological interventions

During the early phases the dependence syndrome, denial of the fact that drug use is problematic may be the rule rather than the exception. Interventions such as motivational enhancement therapy and its related interventions such as brief interventions are particularly effective in patients who display high levels of resistance to change and manifest denial of drug and alcohol problems. During this early phase two techniques are useful to motivate patients towards recovery:

Brief motivational interventions:

This is a suitable intervention for primary care and emergency room practitioners who often can only spend a few minutes with a client. Key principles in counselling patients with addiction problems are non-judgementality and empathy. Described by Bien at.al (Bien et al. 1993), it is summarized by the mnemonic "FRAMES" which entail the following:

F- Feedback: The practitioner provides feedback regarding the negative effects the substance has had on the physical health, interpersonal relations and occupational roles of the client.

R- Responsibility: It is emphasised that the responsibility to stop using remains that of the client.

A-Advice- Advice is given that the cause for many problems relate to drug use and that abstinence or cutting down is advised. Possible options that will facilitate recovery are explored and practical advice is given.

M-Menu for change: Interest is expressed to aid the recovery of the patient and the various options and pathways are discussed such as referral to specialist centres for recovery.

E-Empathy: The counselling style is characterised by a warm and caring style that is empathic and non-judgemental.

S-Self-Efficacy: Hope is instilled by encouragement and emphasising that the patient has the ability and power to change.

Motivational Enhancement Therapy (MET):

This is a counselling intervention that requires a greater deal of skill and training than brief interventions. It is primarily a client-centred approach that emphasizes a non-judgemental empathic style of interviewing and communicating. In this respect it differs from more confrontational techniques such as Minnesota model and 12-step facilitation, although should not be seen as incompatible with such techniques but in fact complementary. The role of the therapist in addiction treatments may vary according to the stage of readiness for change, treatment setting and context and therapists need to be comfortable in adapting this role within the network of role players in addiction treatment that may include the therapist but also family members, employers and other professionals. Motivational enhancement therapies are aimed particularly at persons with high levels of denial and resistance to change. Although client centred, motivational enhancement therapy is not passive but in fact subtly directive in its selective attention to particulars in the clients' communication. Practitioners trained within the medical model often find this approach difficult in the beginning as medical model interviewing often requires more closed ended questioning and more active information gathering exercises.

The following are principles of this technique:

a) Expressing empathy

b) Avoiding argumentation

c) Developing discrepancy

d) Rolling with resistance

e) Enhancing self-efficacy

The aim of this interview technique or communication style is to reflect empathically on the consequences drug taking behaviour has had on the person's life and to develop and point out discrepancies between what the person's life is currently like and what the person aspires to be like. The ultimate goal is to increase the client's ambivalence and develop a sense of discrepancy and cognitive dissonance that in turn will drive motivation to change. A cardinal principal in this communication style is the avoidance of argumentation (i.e., when patients deny or rationalize their drug taking behaviour). Instead resistance to change is met with reflective and empathic listening. Various techniques of reflective listening are used to mobilise initial resistance and thus transforming resistance via self reflection into motivation to change. Self motivating statements are elicited and the therapist empathises with both the part of the client that wants to change and the resistant part, whilst at the same time pointing out discrepancies in the between the clients goals and actual behaviour. It is important to instil hope as self efficacy or the confidence the client has in their ability to effect change, is an important factor in successful recovery.

b) Precontemplative, contemplative and early determination stages:

Pharmacotherapy

The cessation of drug use is accompanied by substance specific withdrawal syndromes. These syndromes typically consist of highly unpleasant symptoms. For certain substances such as alcohol, benzodiazepines, sedative-hypnotics and opioids these syndrome are often more pronounced and requires pharmacological treatment within an inpatient or, in less severe cases, outpatient settings. Most withdrawal regimes consists of substituting the drug of abuse with a agonist medications that act on similar receptor sites as the drug of abuse but that does not have the typical euphoriant side effect profiles. Although several withdrawal regimes exist it is important to measure the presence of a withdrawal syndrome objectively with rating scales and to titrate the dosages of the replacement therapy according to the symptom severity of the withdrawal.

Alcohol withdrawal: Uncomplicated, mild alcohol withdrawal:

Most patients (75-85%) will only experience milder forms of alcohol withdrawal. Symptoms typically consist of nausea, tremors, sweating and tachycardia. Uncomplicated, mild withdrawal can be managed without medication and may only require as needed benzodiazepine treatment on an outpatient basis. Medication should be limited to 5-7 day course of decreasing dose regime. Long acting benzodiazepines are preferable such as chlordiazepoxide or diazepam, with shorter acting agents such as lorazepam and oxazepam reserved only for patients with impaired liver functions. Thiamine replacement therapy should always accompany withdrawal treatment.

Alcohol withdrawal: moderate, severe and complicated alcohol withdrawal. Of all patients with alcohol dependence as many as 25 % of patients may experience symptomatically severe withdrawal syndromes, whilst 5-15% of all alcohol dependence patients may experience complicated withdrawal syndromes. A past history of withdrawal seizures, physical illness such as liver, cardiac or pancreatic disease, hallucinations and psychotic symptoms or delirium tremens should be regarded as indicators of potential complicated withdrawal. Complicated alcohol withdrawal carries a high mortality, is potentially dangerous and is best managed in an inpatient setting equipped and staffed to monitor patients physically on a regular basis. Three approaches on the initiation of benzodiazepine withdrawal regimes are described in the literature (Saitz and O'Malley, 1997). The frontloading approach involves starting the patient on high initial doses (20mg of diazepam) repeated every 2 hours in order to prevent withdrawal. A second approach, the fixed dose regime, involves the prescription of 6hly benzodiazepines (usually 20mg of diazepam), with as needed doses for breakthrough symptoms in between. Alternatively a third approach the "symptom trigger" method involves the regular monitoring for withdrawal symptoms and the administration of benzodiazepines when clinical symptoms reach a threshold above 8 on the CIWA-Ar scale. There is some evidence that initiation of pharmacotherapy after the emergence of symptoms (symptoms trigger approach) produces superior (yet non-significant) outcomes in terms of symptoms relief (Ntais et al. 2005). Practitioners should however be flexible and treat patients according to the severity of symptoms. Under or over treatment with benzodiazepines should be avoided. Intravenous or intramuscular thiamine replacement with additional vitamin B complex should always accompany withdrawal prior to administration of glucose as the administration of glucose prior to thiamine can precipitate a rapid depletion of neuronal thiamine and lead to Wernicke's encephalopathy. Intravenous thiamine administration

should be monitored due to the rare potential complication of an anaphylactic reaction. Antipsychotics should be avoided during the acute withdrawal stage as they can precipitate withdrawal seizures by lowering seizure threshold. In certain circumstances such as delirium tremens antipsychotics can be used cautiously for severe agitation and hallucinations, but care should be taken not to use lower potency agents as these are more likely to precipitate seizures.

Opiate withdrawal and detoxification:

Cessation of opioid use in individuals dependent on opioids is characterised by a highly unpleasant withdrawal syndrome consisting of anxiety, increased sweating, dysphoria, restlessness, craving, irritability, pupillary dilation, lacrimation, rhinorhea, muscle cramps, abdominal cramps, nausea, vomiting, diarrhea, raised blood pressure and increased heart rate (American Psychiatric Association, 2005). Whereas less severe withdrawal syndromes can occur with opioids other than heroin, the following discussion will focus on the detoxification of heroin. In contrast to alcohol withdrawal that represents a condition with considerable morbidity and mortality, opioid withdrawal is rarely ever dangerous. The acute syndrome reaches a peak 48-72 hours after the last dose of opioids and resolves within 7 to 10 days (Mattick and Hall, 1996) The aim of medically assisted opoid withdrawal should always be to prepare patients for ongoing inpatient or outpatient psychosocial rehabilitation. Detoxification of opioids without concomitant rehabilitation serves little purpose. Medications used in the detoxification of opioids are full or partial agonists at the mu opioid receptor site. The most commonly used medications with a good evidence base to support its efficacy are buprenorphine and methadone. Whereas buprenorphine is a partial agonist at mu opioid receptor sites, methadone acts as a full agonist. Both these drugs are long acting and ameliorate the unpleasant withdrawal symptoms associated with cessation of opioid use. Buphrenorphine has a long duration of action making once or even alternate day dosing possible. In contrast to methadone buprenorphine is less sedative and interferes little with QTc interval and cardiac conduction at higher doses. This property together with its ceiling effect at higher dosages (due to lower intrinsic activity as a result of its partial agonist activities) renders this drug safer in overdose and makes it an attractive medication for outpatient, office based detoxification treatment. As buprenorphine can precipitate withdrawal due to its partial agonist actions it is important that this medication be initiated only after symptoms of withdrawal have manifested, usually 12 hours after the last use of heroin.

c) Determination, action and maintenance stages:

Psychological interventions

Twelve-Step Facilitation (TSF):

Twelve step facilitation is a manual based therapy that is aimed at facilitating and encouraging the involvement of patients into community based self-help twelve step programmes such as alcoholics anonymous and narcotics anonymous. Twelve-step facilitation can be delivered in a time limited manner on a weekly basis over 12 weeks or, as in many cases as an ongoing intervention over months to years. The twelve step facilitator therapists are required to have an excellent working knowledge of the twelve step manual as well as the principles that underlie twelve step programs such as AA and NA. This entails reading the AA handbook, twelve step manuals as well as attending several 12 step meetings as a professional guest (in cases where therapists are not recovering addicts). Therapists function as educators that

introduce patients to the 12 step principles, elucidating the structure and functioning of 12-step meetings, the importance of regular attendance and the role of sponsors. Therapists should be actively encouraging participation in 12-step meetings and explore patient's views of 12-step principles such as the pertinent role of spirituality and the notion of a higher power. Central to twelve step facilitation is the notion that addiction is a disease with a physical, emotional as well as spiritual component. In the 12-step model cure from addiction is not viewed as a realistic option but rather management of an ongoing chronic illness, with abstinence from drugs and alcohol viewed as a central treatment goal. Surrender to a higher power, which may be symbolized by treatment principles, structures and philosophy or more spiritual notions such as God, is viewed as a critical step in treatment. Patients are required to keep a diary of their attendance of meetings and the issues discussed at meetings. In turn therapists confront patients in a non-judgemental manner should there be signs of resistance or denial of drug and alcohol related problems. Denial may manifest in non attendance of meetings and rationalizations as to why attendance is not possible. It is important for therapist to explore patient's experiences of 12-step meetings in order to identify each patient's unique views and beliefs about twelve step programs. This will enable therapists to explore problems relating to denial or irrational or erroneous beliefs about 12-step programs and make suggestions as to how this can be addressed. Twelve step programs have been found to be as effective as cognitive behavioural and motivational enhancement treatments in reducing alcohol intake at 1 and 3 years follow up in the large multisite randomized controlled trial, project MATCH. In turn twelve step facilitation has shown somewhat superior outcomes in promoting abstinence and higher AA and NA attendance rates in aftercare settings (Humphreys, 1999).

CBT for relapse prevention:

Cognitive behavioural therapy is based on the principles of learning theory and has as one of its main targets to promote cognitions and behaviour that disrupt the cycle of learned drug taking behaviours that is encoded via the mechanisms of classical and operant conditioning. It is a highly structured; time limited (12-24 weeks) therapy in characterised by a collaborative client therapist relationship. It forms part of the active treatment and maintenance phases of the treatment cycle, with the principal objective being that of acquiring the necessary skills to prevent relapses into drug taking behaviour. Sessions are highly structured in that time is devoted first on feedback and homework assignments, then on didactic discussion of skills and behaviour followed by setting goals and targets. An important tool in therapy is functional analysis of behaviour that is associated with drug taking. In this analysis internal (emotional and cognitive) and external (environmental) triggers are identified and skills and techniques are then acquired on how to manage and deal with these triggers. Aspects of the functional analysis include identifying thoughts and feelings associated with internal triggers such as craving as well as environmental triggers that may drive dysfunctional beliefs about drug use. Skills training involve the learning of techniques to cope with craving and social pressures and may include distraction techniques and assertiveness training. CBT has been demonstrated to be effective as a relapse prevention treatment across a wide variety of substance use disorders including cocaine, alcohol, cannabis, nicotine and heroin addictions (Magill and Ray, 2009). CBT has also been shown to offer additional benefits for patients with co-occurring psychiatric disorders such as depression. Findings from Project Match, a large multicentre randomised controlled trail in patients with alcohol dependence investigating the efficacy of twelve step facilitation (TSF), cognitive behaviour therapy (CBT) and motivational enhancement therapy (MET), demonstrated CBT to be efficacious

in reducing drinking (Project MATCH Research Group, 1998a; Project MATCH Research Group, 1998b). An important effect demonstrated by earlier studies of CBT for drug addiction is the lingering effect after therapy has been terminated (Carroll et al. 1994). This effect is particularly useful when CBT is used in combination with behavioural treatments such as contingency management that often show potent effects early on in treatment, which subsides wanes as treatment is discontinued (Rawson et al. 2006). In addition recent research has demonstrated superior outcomes for CBT in comparison to interpersonal therapy (IPT) in patient with cocaine dependence (Carroll et al. 2004). An important potential active ingredient for CBT efficacy has been shown to be high compliance with additional session and homework assignments. Thus patients who comply more diligently with home work assignments have been shown to have superior outcome in CBT (Carroll et al. 1994; Carroll et al. 2005). Although treatment programs may be eager to roll out manualized forms of CBT treatment, therapist training associated with active session to session direct personal supervision has been demonstrated to be associated significantly higher fidelity to CBT criterion standards.

Combined psychosocial modalities: matrix model

The matrix model of treatment is an intensive, manualized, outpatient based treatment model for addictive disorders. Although it originated during the cocaine epidemic during the 1980's in the United States, it has been developed as a treatment for methamphetamine addiction as well as other non-stimulant addictions (Obert et al. 2000; Rawson et al. 1995). This eclectic treatment model incorporates various evidence based psychosocial interventions such as motivational enhancement therapy, 12-step facilitation, cognitive behavioural therapy, contingency management and family therapy. A typical treatment program consists of a highly structured 4 month, 3 times per week intensive outpatient based program followed by somewhat less structured 8 month continuing care program. Treatments are structured according to the stage of recovery and include early recovery groups in the early recovery stages and relapse prevention and social support groups in the more advanced stages. Information about the nature of addiction and the recovery process is also given early on in the treatment and a family psycho-education group forms a critical part of treatment. Early recovery groups focus on ways patients can attain abstinence early on in treatment. Relapse prevention groups focus on identifying external and internal triggers for relapse as well as methods to cope with such triggers. Social support groups are aimed at helping clients develop of social and interpersonal supports that are non drug users. An important part of the program involves facilitation into 12-step self help groups. Individual counselling and support is also received in parallel with group therapy. In contrast to more confrontational inpatient based models, the therapist style is non-confrontational and firmly based on motivational interviewing principles. Therapists are however not passive and actively pursue non-compliant patients in a non-confrontational caring manner. Weekly urine tests are conducted and negative tests are positively re-inforced with rewards. Some programs also make use of structures contingency management schedules of reward (Obert et al. 2002).

d) Determination, action and maintenance stages:

Pharmacological interventions

Alcohol dependence

Disulfiram:

Disulfiram is an irreversible inhibitor of the enzyme acetaldehyde dehydrogenase. Administration of disulfiram causes an accumulation of acetaldehyde, a toxic breakdown product of in the metabolism of alcohol. This results in a highly unpleasant reaction characterised by facial flushing, severe nausea and vomiting, hypotension and headaches. This reaction is thought to be a powerful negative reinforcer promoting abstinence. Studies have however shown that the efficacy of this medication is highly dependent on compliance with this drug, which can be very poor (Fuller et al. 1986). More recent research has shown that supervised consumption of disulfiram by family members of addicts has improved outcomes (De Sousa et al. 2008; Laaksonen et al. 2008). Therapy with disulfiram has to be initiated cautiously as this medication is contraindicated in alcohol dependent individuals with liver, kidney and cardiac conditions. Disulfiram treatment has also been reported to be associated with the development of psychotic symptoms.

Naltrexone:

One postulated mechanism whereby alcohol produces its reinforcing effects is via the increased release of endogenous opioids. Endogenous opioid secretion increases the release of dopamine directly via stimulation of the nucleus accumbens or indirectly by inhibiting the tonically inhibitory effect of GABA neurons on dopamine neurons within the nucleus accumbens (Gianoulakis, 2009). Evidence from randomized controlled trials and meta-analyses has supported the use of naltrexone a mu opiate receptor antagonist in the maintenance treatment of alcohol dependence (Srisurapanont and Jarusuraisin, 2005). There is also evidence that naltrexone can help to prevent a lapse into drinking from turning into a full blown relapse. As an antagonist of mu opiate receptors naltrexone blocks the stimulation of opiate receptors by beta endorphins which in turn is postulated to result in less dopamine release in the nucleus accumbens. Via this mechanism the positive reinforcing euphoriant effects of alcohol is attenuated and type I craving is diminished. Naltrexone is well tolerated in the majority of patients. Contraindications include abnormalities in liver function and the comorbid presence of opioid dependence. Monitoring requirements include baseline and follow up liver enzymes. Concurrent use of medications that are potentially hepatotoxic should be avoided (such as disulfiram). Use with opioid containing analgesics is contraindicated. Naltrexone is also available in long acting depot formulation (XR-NLX) for once monthly administration.

Acamprosate:

Acamprosate is related to the amino acid taurine. Acamprosate modulates hyperglutamatergic states characteristic of acute and protracted alcohol withdrawal via its inhibitory action on excitatory NMDA receptors and facilatatory action on GABA function. The prolonged withdrawal stage is characterised by increased excitatatory glutamatergic neurotransmission due to NMDA receptor upregulation that takes place during the intoxication phases in the presence of high alchohol levels. Via its inhibitory action on NMDA receptors acamprosate curbs negative or type 2 craving associated with unpleasant withdrawal symptoms. Studies have demonstrated that acamprosate is effective in preventing relapse into heavy drinking. This effect may be more pronounced in patients who are more motivated to remain abstinent (Johnson et al. 2007; Johnson et al. 2008).

Topiramate:

Other candidate drugs in the maintenance treatment of alcohol dependence include topiramate, a drug that is thought to both enhance GABAA inhibitory activity over the positive reinforcing effects of dopamine in the nucleus accumbens (type I craving) and at the same

time attenuates glutamatergic hyperactivity via its action on AMPA glutamatergic receptors (type 2 craving). In turn it is thought that the decrease of glutamatergic activity results in decreased dopamine release in the nucleus accumbens (Kenna et al. 2009). Two randomized controlled trials, one of which is a multisite trial, have demonstrated the superior efficacy of topiramate over placebo on a number of outcome measures such as time abstinent from drinking, level of self reported drinking, compulsive cravings for alcohol and improved physical and psychosocial wellbeing (Johnson et al. 2003; Johnson et al. 2007; Johnson et al. 2008).

Baclofen:

In recent years baclofen, a GABAB receptor agonist, has received increasing attention in pharmacotherapy trials for alcohol maintenance (Addolorato et al. 2009). Due to the fact that it is not metabolized in the liver makes it an attractive alternative for patients with alcohol dependence and existing liver damage (Garbutt and Flannery, 2007). Three randomized controlled trails have been conducted to date with two showing significant superiority over placebo in reducing alcohol intake and prolonging periods of abstinence from alcohol (Addolorato et al. 2002; Addolorato et al. 2007; Garbutt et al. 2007). A third trial conducted in the US failed to replicate these findings and further research is necessary to clarify the role of baclofen in the treatment of alcohol dependence (Garbutt et al. 2007).

Opioid dependence:

Prospective cohort studies have demonstrated that long term abstinence based community residential rehabilitation programmes can be successful for opioid dependent patients with up to 50% achieving abstinence at 5 year follow up (Gossop et al. 2003). Nevertheless a subgroup of patients with severe heroin dependence is unlikely to succeed with traditional abstinence based approaches and may require harm reduction approaches that consist of opioid substitution maintenance prescribing. The primary aim of substitution maintenance treatment is to reduce the use of illicit heroin and in turn the associated morbidity and criminal behaviours that often accompany heroin addiction. Table 6 summarizes some of the goals of opioid substitution therapies.

Table 6. Aims of opioid substitution prescribing

1. Reduction of illicit heroin use
2. Reduction of criminal behaviour accompanying heroin use
3. Reduction of morbidity associated with heroin use such as risky sexual practices and needle sharing (HIV, Hepatitis B and C transmission)
4. Reduction of mortality associated with heroin overdoses
5. Creation of a environment conducive to addressing social and occupational problems

During substitution maintenance treatment patients are given the opportunity to reconstruct their lives and improve their psychosocial and occupational functioning in order to obtain greater stability. Maintenance treatments can be time limited over 12 to 24 months but may be a treatment option over many years.

The main medications used in substitution maintenance programs are methadone, a full mu receptor agonist and buprenorphine, a partial mu receptor agonist. Research has shown

that methadone, in particular high dose methadone maintenance is somewhat superior to buprenorphine in reducing illicit heroin use. Nevertheless as the side effect profile of methadone includes mild oversedation and somnolence; both agents are recommended as treatment options in maintenance programs. Substitution maintenance programs have to adhere to certain standards to be effective. These standards include staff trained and experienced in prescribing substitution medications. Daily supervised consumption including a full pre-treatment medical workup (including HIV and Hepatitis testing) is mandatory for all patients initiated on substitution therapies. Daily supervised consumption is less critical in patients treated with burprenorphine or buprenorphine-naloxone combinations, however still recommended in the early stabilization phase of treatment. Random urine tests testing for heroin is also mandatory. A pre-treatment contract between the treating doctor and patients stipulating the consequences of a positive urine tests is also important. One particular clinical problem is the injection of substitution medicines to obtain a high or the selling of these medicines (called diversion) to raise funds for illicit heroin. In some countries electronic methadone prescription monitoring services have been launched to prevent patients from obtaining prescriptions more than once at different pharmacies. Another strategy to counter diversion and injection practice is the use of Suboxone, a combination of buprenorphine (opioid agonist) and naloxone (opioid antagonist) in a 4:1 ratio. When taken sublingually the bioavailability of naloxone is not sufficient to lead to any clinical effect. However in the context of diversion practices and intravenous abuse of substitution medicines, naloxone has a high bioavailability leading to the induction of unpleasant withdrawal reactions and therefore acts as a discouragement for injection practices.

Patients on maintenance treatment may prematurely want to discontinue their opioid substitution medication in order to become drug free and independent. Each individual case needs to be carefully reviewed in terms of the particular clients' strengths and ongoing risks of relapse. Factors that can contribute to relapse such as instability in interpersonal, occupational or living circumstances need to borne in mind when considering suitability to wean patients from opioid substitution medications.

6.0.5 Suggested reading

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7 Personality Disorders

7.1 Introduction

7.1.1 Background

Treating psychopathology requires an understanding of personality. Research on the DSM and ICD disorders is making it increasingly clear that:

1. anxiety, depression, eating disorders, substance abuse, sexual disorders, and other DSM Axis I Clinical Syndromes occur more often in the context of Personality Disorders (PDs) (Shea, Widiger, & Klein, 1992);

2. patients with multiple clinical syndrome diagnoses often have PDs (Newman, Moffitt, Caspi,& Silva, 1998); and

3. even those patients who lack personality disturbances severe enough to warrant a DSM or ICD personality diagnosis often have clinically significant pathology, such as difficulties with intimacy, management of aggression or self-assertion, rejection-sensitivity, etc (Westen, 1997).

There is little question that inclusion of a PD axis in the DSM and ICD, and its refinement through two decades of research, has been a crucial step in the evolution of more clinically and empirically useful diagnostic manuals. Knowing that a patient has major depression is certainly important, but adding the "qualifier" that the patient also has borderline PD is equally important because it has significant implications for prognosis and treatment.

PDs have historically been in a tangential position among diagnostic syndromes, never having achieved a significant measure of recognition in the literature of either clinical psychiatry or abnormal psychology. Prior to the DSM-III and ICD-8, they were categorized in the official nomenclature with a mélange of other miscellaneous and essentially secondary syndromes. Today, PDs occupy a place of diagnostic prominence, having been accorded a contextual role in the multiaxial schema of the DSM. Personality pathologies comprise one of two required "mental disorder" axes in the DSM. Henceforth, clinicians must not only assess the patient's current symptomatology, indicated on Axis I, but also evaluate those pervasive features which characterize the patient's enduring personality pattern, recorded on Axis II. In effect, the revised American multiaxial format requires that symptom states no longer be assessed as clinical entities isolated from the broader context of the patient's lifelong style of relating, coping, behaving, thinking, and feeling - that is, his or her personality.

Personality and its disorders are regarded as a potential diathesis (Tyrer, 2007). There are clinical theorists who assert that it is the patient's personality that should be evaluated first; only secondarily should the patient's clinical state be considered. There are substantive reasons for attending to the PDs first, beyond the pragmatics of adhering to official nosological

requirements. Lifelong personality traits appear to serve as a substrate, as well as a context for understanding more florid and distinct forms of psychopathology. Since the early 1960s, most societies have been increasingly committed to the early identification and prevention of mental disorders. This emphasis has led clinicians to attend to both premorbid behavioural signs and the less severe variants of emotional disturbance. Ordinary anxieties, minor personal conflicts, and social inadequacies are now seen by many clinicians as the forerunners of more serious problems. A significant impetus to this movement is the emergence of community health centres whose attentions are directed to the needs of the less seriously disturbed. As a result of these developments, the scope of clinical psychopathology was broadened far beyond its historical province of "Hospital Psychiatry." As a field, it now encompasses the full spectrum of mild to severe mental disorders. With personality as a contextual foundation, diagnosticians have become more proficient in understanding personality dynamics and can more clearly trace the sequences through which both subtle and dramatic clinical symptoms unfold.

7.1.2 Social Costs

PDs have been estimated to affect at least 10% of the population, and constitute a large percentage of the patients seen by psychiatrists. Yet unlike other diagnoses, PDs may or may not be associated with subjective symptoms. While some categories show high comorbidity with symptomatic diagnoses such as anxiety and depression, some PDs produce distress in other people rather than in the patient. But in either case, the overall functioning of patients with PDs is often marginally social, comparable in many cases to levels seen in patients with chronic conditions such as schizophrenia.

Numerous studies suggest that PDs are underappreciated causes of social cost, morbidity, and mortality. PDs are associated with crime, substance abuse, disability, increased need for medical care, suicide attempts, self-injurious behaviour, assaults, delayed recovery from Axis I and medical illness, institutionalization, underachievement, underemployment, family disruption, child abuse and neglect, homelessness, illegitimacy, poverty, STDs, misdiagnosis and mistreatment of medical and psychiatric disorders, malpractice suits, medical and judicial recidivism, disruption of psychiatric treatment settings, and dependency on public support. The amount of social cost and disruption caused by the PDs is disproportionate to the amount of attention it gets in the public consciousness, in government research funding, in medical school education or even in psychiatric residency training And no less important than dealing with the social costs of personality disorders is the potential value inherent in preventive programs designed to enhance personality resilience and adaptive capacities.

7.1.3 Definitions

Personality is seen today as a complex pattern of deeply embedded psychological characteristics that are largely nonconscious and not easily altered, expressing themselves automatically in almost every facet of functioning. Intrinsic and pervasive, these traits emerge from a complicated matrix of biological dispositions and experiential learnings, and ultimately comprise the individual's distinctive pattern of perceiving, feeling, thinking, coping, and behaving.

Personality is the patterning of characteristics across the entire matrix of the person. Rather than being limited to a single trait, personality regards the total configuration of the person's characteristics: interpersonal, cognitive, psychodynamic, and biological. Each trait reinforces the others in perpetuating the stability and behavioural consistency of the total personality structure. For the personality disorders, then, causality is literally everywhere. Each domain interacts to influence the others, and together, they maintain the integrity of the whole structure.

Personality disorders are not diseases or disorders in the usual medical disease sense. Rather, PDs are theoretical constructs employed to represent varied styles or patterns in which the personality system functions maladaptively in relation to its environment. When the alternative strategies employed to achieve goals, relate to others, and cope with stress are few in number and rigidly practiced (adaptive inflexibility), when habitual perceptions, needs, and behaviours perpetuate and intensify pre-existing difficulties (vicious circles), and when the person tends to lack resilience under conditions of stress (tenuous stability), we speak of a clinically maladaptive personality pattern, that is, a PD.

7.1.4 Differentiating Normality and Abnormality

Distinctions between normality and pathology are largely social constructions or cultural artefacts. Normality and pathology must be viewed as relative concepts; they represent arbitrary points on a continuum or gradient - no sharp line divides normal from pathological behaviour. Among diverse and ostensibly content- and culture-free criteria used to signify normality are a capacity to function autonomously and competently, a tendency to adjust to one's social milieu effectively and efficiently, a subjective sense of contentment and satisfaction, and the ability to self-actualize or to fulfil one's potentials throughout the life span into one's later years.

PDs were noted either by deficits among the preceding or by the presence of characteristics that actively undermine these capacities. Perhaps these criteria are too westernized or Eurocentric to be universal. In some Asian cultures, for example, where the individual is expected to subordinate individual ambitions to group consensus, the capacity to function autonomously might be praiseworthy, but the desire to do so is not. The traits which compose a number of personality styles are likely in certain historical periods or cultures, such as contemporary Western societies, to promote healthy functioning (e.g., Histrionic, Compulsive, Narcissistic traits). Similarly, in this society, there are personality styles and traits that are highly conducive to pathological functioning (e.g., Avoidant, Dependent, Masochistic). There are other personality patterns (e.g., Schizotypal, Borderline, Paranoid) which have a very small probability of falling at the normal end of the continuum in almost all cultures.

7.1.5 Historic antecedents

The interest in the description of individual differences is very old. In Theophrastus' Characters, written in the 3rd century BC, 32 different types of human beings are described, some of them familiar to clinicians nowadays (Theophrastus, 1998). In the fourth century B.C. Hippocrates concluded that all disease stemmed from an excess of or imbalance

among four bodily humours: yellow bile, black bile, blood, and phlegm. Hippocrates identified four basic temperaments, the choleric, melancholic, sanguine, and phlegmatic; these corresponded, respectively, to excesses in yellow bile, black bile, blood, and phlegm. Although the doctrine of humours has been abandoned, giving way to scientific studies on topics such as neurohormone chemistry, its terminology and connotations still persist in such contemporary expressions as being sanguine or good humoured.

Along the 19th century the concept of pathological personality was forged. Pinel in 1809 described his manie sans délire, that is to say, mental illness without symptoms of illness, to which he later on also referred as folie raisonnante, that is to say, madness without insanity.

J.A. Koch who proposed, replacing the established label moral insanity, with the term psychopathic inferiority Koch used the term psychopathic, a generic label employed to characterize all personality diagnoses until recent decades, to signify his belief that a physical basis existed for these character impairments. The prime psychiatric nosologist at the turn of the century, Emil Kraepelin, did not systematize his thinking on PDs, but in his efforts to trace the early course of these syndromes, Kraepelin "uncovered" two premorbid types: the "cyclothymic disposition," exhibited in four variants, each inclined to maniacal-depressive insanity; and the "autistic temperament," notably disposed to dementia praecox.

The best-known European classification of disordered personalities was proposed by Kurt Schneider. Schneider differed from many of his contemporaries, most notably the prime modern constitutionalist The best-known and perhaps most fully conceptualized of PDs are those formulated by psychoanalytic theorists. Their work was crucial to the development of an understanding of the causal agents and progressions that typify the background of these disorders. It was Sigmund Freud and his younger associates, Karl Abraham and Wilhelm Reich, who laid the foundation of the psychoanalytic character typology h.

Although numerous analytic theorists have continued to contribute to the study of character, the contemporary work of Otto Kernberg deserves special note. Taking steps to develop a new psychoanalytic characterology, Kernberg constructed a framework for organizing personality types in terms of their level of severity to speak of "higher, intermediate and lower levels" of character pathology; both intermediate and lower levels are referred to as "borderline" personality organizations.

Note should be made of another productive personologist who utilized a mathematical/-factorial approach to construct personality dimensions, namely Raymond Cattell (Cattell, RB (1965)). His research has led him to identify 16 primary traits, which he then arranged in sets of bipolar dimensions that would undergird personality types. Other contemporary quantitative contributors include Peter Tyrer (Tyrer, 1988) and W. John Livesley (Livesley, 1987).

In a model which seeks to draw on genetic and neurobiologic substrates, Robert Cloninger has proposed a complex theory based on the interrelationship of several trait dispositions. Another biosocial model using three pairs of evolutionary polarities as a basis is one developed by Theodore Millon. Here, he derived a PD taxonomy that subsumed the dependent, independent, ambivalent, and detached coping styles with an activity-passivity dimension. Notably, in their recent work, numerous theorists have begun to turn their attention to positive mental health, speaking of personality resilience and adaptive capacities.

7.1.6 The Current Official Systems, ICD-10 and DSM-IV TR

Two classificatory systems of mental disorders are recognized internationally today, namely, the Diagnostic and Statistical Manual of Mental Disorders - 4th Edition-Text Revised (DSM-IV-TR)19 and the International Classification of Mental and Behavioural Disorders (ICD-10)20. Personality disorders are given important weight in both classifications. The DSM-IV-TR places them in its separate Axis II (this classification comprises five such axes). The personality disorders in the DSM are grouped into three clusters, based essentially on empirical descriptive similarities; this cluster grouping has not (and maybe never will be) been satisfactorily validated but its widespread use indicates a frequent wish to reduce the number of categories. Cluster A includes paranoid, schizoid and schizotypal personality disorders (the so-called odd or eccentric individuals), Cluster B comprises antisocial, borderline, histrionic and narcissistic PDs (the ostensible dramatic, emotional or erratic individuals), and Cluster C includes avoidant, dependent and obsessive-compulsive PDs (anxious/fearful individuals). A last category, "PD not otherwise specified," comprises disorders of personality that do not fulfil the specific criteria for any of the above individual PDs.

The ICD-10 Classification includes a single section covering all personality abnormalities and persistent behavioural disturbances. This is separated into specific named personality disorders, mixed and other personality disorders, and enduring personality changes. The individual personality disorders are paranoid, schizoid, dissocial, emotionally unstable (impulsive and borderline types), histrionic, anxious (avoidant), anankastic and dependent ones. Two more categories are "other specific PDs" and "PD, unspecified." The ICD classification is similar to that of DSM-IV, although differences are noteworthy. For example, the borderline PD of the DSM-IV is subsumed as one of the two emotionally unstable disorders in ICD-10, the obsessive-compulsive adjective in DSM-IV is retained as "anankastic" in ICD-10, and avoidant personality disorder is only a partial equivalent of the ICD-10 anxious personality disorder. Two more disorders included in the official section of the DSM-IV are excluded from ICD-10; schizotypal disorder is a variant within the schizophrenia spectrum of conditions in ICD-10 and narcissistic personality disorder is only mentioned in the section on "other specific PDs" in ICD-10, without any specific criteria noted for this diagnosis. The ICD-10 contains other general categories that refer to PDs that have no counterpart in the DSM-IV, such as "mixed disorders" and "other disorders of adult personality and behaviour."

7.1.7 Diagnostic assessment

Five broad sources of information are available to help describe the clinical problem; each has its own advantages and limitations.

The first comprise clinical interviews and observations; the clinician observes and asks the questions and the subject responds verbally, often in a free-form style. The clinician is free to follow any particular line of questioning desired and usually mixes standard questions with those specific to the current problem.

The second is structured or semi-structured interviews. Open ended, free form style clinical interviews may provide insufficient information to assess the different personality disorders. Interviewer- administered interviews, structured or semi-structured, systematically address and assess each personality disorder criteria with standard questions or probes. The most

often used are International Personality Disorders Examination (IPDE), Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) and

The third second are formal rating scales and checklists; a person familiar with the subject completes those forms in order to provide an objective perspective. Rating scales and checklists often serve as a memory aid, ensuring that everything relevant to the disorder is included in developing a treatment plan. Rating scales usually have more items than the diagnostic criteria for the same syndrome and are usually held to a higher standard of scientific rigor. Because they have more items, they provide more fine-grained measurements, but they also take more time to complete. For example, the revised Psychopathy Checklist (PCL-R) consists of 20 items, whereas the DSM-IV offers only seven criteria for the diagnosis of antisocial PD. Although the PCL-R is widely used in the study of psychopathy, few rating scales exist for use with other PDs.

The third source is the self-report inventory; subjects literally report on themselves by completing a standard list of items. Because self-reports represent the subject's own responses, they can be especially valuable in quickly identifying clinical symptoms. Unless the individual is violent or psychotic, a self-report inventory can be given at any point during the clinical process, often with minimal supervision. A profile obtained at the beginning of therapy, for example, can be used as a baseline to evaluate future progress. A number of other self-report instruments are available. The Tridimensional Personality Questionnaire (TPQ)„ Millon Clinical Multiaxial Inventory (MCMI-III), Neuroticism-Extroversion-Openness- Personality Inventory Revised (NEO-PI-R), The Dimensional Assessment of Personality Pathology-Basic Questionnaire (DAPP), The Schedule of Nonadaptive and Adaptive Personality (SNAP) are the most often used self-report assessment instruments.

The fourth source of information is projective techniques, an attempt to access unconscious structures and processes that would not ordinarily be available to the subject at the level of verbal report. These techniques seek to draw out internal, and frequently unconscious, influences on behaviour by presenting the subject with inherently unstructured, vague, or ambiguous situations. The Rorschach Inkblot Test is the classic example. The subject is presented with a series of 10 blots in turn and asked to report what he or she sees. The Thematic Apperception Test uses pictures of various interpersonal situations. The subject constructs a story to explain what is happening in the picture, what led up to these events, and how matters will end. Because projective instruments are time-consuming and not widely regarded as being as psychometrically sound as self-report inventories, their use has waned in recent years, especially with the economic constraints of managed care.

Finally the use of inmates (informants) of the subject, perhaps a spouse, teacher, parent, or good friend, someone who can provide perspective on the problem, might also be considered another important source of information.

7.1.8 Problems in the current classification

The official classification systems reflect a variety of personality related issues that are likely to be solved in the near future with the revision of both systems.

First, there is the question of the retention of personality disorders on a different axis (Axis II) from that of clinical syndromes (Axis I) in the DSM-IV. The division between Axis I and Axis II seems to some to be arbitrary and not justified adequately.

A second persistent problem is the classificatory status of the individual categories of personality disorder. There is great overlap between the criteria for diagnosing personality disorders in both DSM-IV and ICD-10 and this seriously compromises their validity as separate disorders. Clear differentiation between the disorders is often difficult and many individuals diagnosed with a personality disorder have several other personality disorders that do not always appear to be fundamentally different.

A third issue is the overlap of some personality disorders with disorders in Axis I. An example is the relationship between avoidant PD and generalized social phobia, both of which address the same group of symptoms without a clear distinction between them. Although still included in the Appendix B of DSM-IV, there seems to be a similar problem between depressive personality disorder (Axis II) and dysthymia (Axis I).

A fourth question is how many personality disorders deserve separate description in the two classification systems? It is also uncertain what type of criteria should constitute the building blocks of personality disorder and how many of them are needed for each diagnosis. Both classifications rest mainly on historical traditions and committee consensus rather than on empirical data or well-constructed theoretical grounds. Many of the assumptions of each classification are implicit or covert and need to be exposed so that diagnosis can be made consistently and subjected to systematic testing. Fifth, there are also many questions about the division between "normal" personality and personality disorders that need answering and whether it is wise to have a division at all.

Sixth, another major controversy in the field is the categorical/dimensional/prototypical controversy, to which we will turn shortly. A further issue is the polythetic criterion lists used in current classification systems; these produce considerable intragroup variability such that two people with the same diagnosed PD may display very different features because they score for different sections.

Finally seventh , as already mentioned, PDs are tied to cultural variables to a much greater extent than the clinical disorders in Axis I, creating difficulties when diagnosing this kind of disorders across different cultures, a topic we will also address in a later section.

Given the need for a clear unambiguous official classificatory system for personality disorders and the dissatisfaction with the current two systems, there are likely to be important changes in the classification of personality disorders in DSM-V and ICD-11. Perhaps the most important question is "how do we improve the clinical utility of the classification of personality disorders so that it is recognised to be helpful in decision-making at all levels?"

7.2 Each of the Personality Disorders

The Personality Disorders are grouped into three clusters based on descriptive similarities.

Cluster A includes paranoid, schizoid and schizotypal personality disorders (the so-called odd or eccentric individuals), Cluster B comprises antisocial, borderline, histrionic and

narcissistic PDs (the ostensible dramatic, emotional or erratic individuals), and Cluster C includes avoidant, dependent and obsessive-compulsive PDs (anxious/fearful individuals).

A general definition of personality disorders are provided in DSM-IV-R and in ICD-10. It can be useful to psychiatrists and clinical psychologists, because the most common diagnosis in clinical practice is the diagnosis "not other specified" (Clark et al. 1995)

General criteria diagnostic criteria for a Personality Disorder (ICD-10)

A specific personality disorder is a severe disturbance in the characterological constitution and behavioural tendencies of the individual, usually involving several areas of the personality, and nearly always associated with considerable personal and social disruption. Personality disorder tends to appear in late childhood or adolescence and continues to be manifest into adulthood. It is therefore unlikely that the diagnosis of personality disorder will be appropriate before the age of 16 or 17 years. General diagnostic guidelines applying to all personality disorders are presented below; supplementary descriptions are provided with each of the subtypes.

Diagnostic guidelines

Conditions not directly attributable to gross brain damage or disease, or to another psychiatric disorder, meeting the following criteria:

(a) markedly dysharmonious attitudes and behaviour, involving usually several areas of functioning, e.g., affectivity, arousal, impulse control, ways of perceiving and thinking, and style of relating to others;

(b) the abnormal behaviour pattern is enduring, of long standing and not limited to episodes of mental illness;

(c) the abnormal behaviour pattern is pervasive and clearly maladaptive to a broad range of personal and social situations;

(d) the above manifestations always appear during childhood or adolescence and continue into adulthood;

(e) the disorder leads to considerable personal distress but this may only become apparent late in its course;

(f) the disorder is usually, but not invariably, associated with significant problems in occupational and social performance.

For different cultures it may be necessary to develop specific sets of criteria with regard to social norms, rules and obligations. For diagnosing most of the subtypes listed below, clear evidence is usually required of the presence of at least three of the traits or behaviours given in the clinical description.

Cluster A

For additional information and references see Module II in Simonsen E, Ronningstam E, Millon T (Eds). (2007). WPA ISSPD Educational Program on Personality Disorders. www.wpanet.org/education/education.shtml: Henning Sass & Reinhild Schwarte: Schizoid

Personality Disorder (pp. 129-133) Schizoid Personality Disorder. Svenn Torgersen: Schizotypal Personality Disorder (pp. 134-141). Elizabeth Iskander & Larry J. Siever. Paranoid Personality Disorder (pp. 110-116)

Schizoid Personaliy Disorder
(partly adopted from Henning Sass & Reinhild Schwarte)

Case vignette

Jacob is a 26 years old man. Despite extraordinary intelligence John was not able to complete or participate in any educational program. He wanted to have a normal life with a family and friends, but thought that he was rootless and he felt that other people thought that he was peculiar or odd. He felt that he was outside. As a child he went to various schools because his parents moved around. He was thought of as a lonely wolf and did not participate in the social life or games of sports with his peers. During school class he was often absent minded being absorbed in his own thoughts and fantasies. From around the age of thirteen he became interested in computers and was quite advanced in his understanding of mathematics. He became exceedingly isolated with his computer as his sole companion.

This vignette schizoid personality illustrates the difficulties how to establish a stable relationship to significant others like peers and family. Often it is regarded as unusual that a person with schizoid personality disorders complains by himself or herself to be isolated. Many schizoid patients, in the contrary, claim to be quite satisfied with their loneliness and it is quite unusual that he wish to have a family. Also schizoid persons usually accept their situation or even deny any desire for closer relationships.

Clinical Description

Diagnostic Criteria ICD-10

F60.1 Schizoid personality disorder

Personality disorder meeting the following description:

(a) few, if any, activities, provide pleasure;

(b) emotional coldness, detachment or flattened affectivity;

(c) limited capacity to express either warm, tender feelings or anger towards others;

(d) apparent indifference to either praise or criticism;

(e) little interest in having sexual experiences with another person (taking into account age);

(f) almost invariable preference for solitary activities;

(g) excessive preoccupation with fantasy and introspection;

(h) lack of dose friends or confiding relationships (or having only one) and of desire for such relationships;

(i) marked insensitivity to prevailing social norms and conventions.

Excludes: Asperger's syndrome (F84.5) delusional disorder (F22.0) schizoid disorder of childhood (F84.5) schizophrenia (F20. -) schizotypal disorder (F21)

The central feature of Schizoid Personality Disorder (SPD) is a pattern of pervasive social detachment and a narrow range of emotional expression in social settings. The DSM-IV criteria for SPD differ in detail in three criteria from the ICD-10 diagnostic criteria. The both describe the SPD by seven criteria, of which at least three must be applicable. The SPD is most clearly defined within relationships. Individuals with this disorder are characterized by a profound defect in their ability to form personal relationships or to respond to others in an emotionally meaningful way and appear to lack a desire for intimacy. They are introverted, aloof, and seclusive, and select activities that do not include much interaction with others. This style of life easily results in social isolation.

Differential Diagnosis

The differential diagnosis of SPD includes:

1. a normal preference for solitary pursuits that does not meet the criteria for schizoid personality disorder;

2. schizophrenia (in which further characteristic negative or positive symptoms occur); The SPD appears to characterize the negative symptoms of schizophrenia, e.g., social, interpersonal, and affective deficits like little affect, low energy, anhedonia, diffidence about, shyness in, or detachment from relationships.

3. schizotypal personality disorder (in which there are cognitive and perceptual distortions); In contrast to the schizotypal personality disorder the SPD does not include psychotic-like cognitive/perceptual distortions.

4. paranoid personality disorder (in which the patient displays suspiciousness and paranoid ideations);

5. avoidant personality disorder (in which the patient has a fear of being embarrassed or inadequate, with excessive anticipation of rejection);

6. obsessive-compulsive personality disorder (in which there may be apparent social detachment that arises from devotion to work and discomfort with emotions; capacity for intimacy is usually preserved);

7. disorders of more severely impaired social interaction, stereotyped behaviours and limited interests (e.g., autistic disorder, Asperger's disorder);

8. personality change caused by a general medical condition (e.g., temporal lobe epilepsy); personality symptoms derived from chronic substance use (Sass, 2007).

Comorbidity

The most frequent co-occurring personality disorders with SPD are schizotypal and avoidant personality disorders and to a lesser degree paranoid, antisocial and borderline personality disorders (Kalus et al. in Livesley, 1995, p.65). The highest co-occurrences may perhaps be because of the high overlap between the two criteria sets. The SPD and the schizotypal personality disorder, for example, share the important criteria of social isolation and restricted affect. Also the avoidant personality disorder may seek isolation, but individuals with SPD will tolerate the separation with comfort, while individuals with avoidant personality disorder will be distressed and lonely. SPD can an antecedent disorder to schizophrenia, major depression, dysthymia or a delusional disorder. Further it shows high comorbidity

with social phobia and agoraphobia. If people with SPD are detached from a supportive family they often become involved with drugs and alcohol.

Prevalence

SPD is uncommon in clinical treatment settings. SPD is diagnosed more frequently in males who seem to be more impaired than females with SPD.

Etiology

The etiology of SPD has not been established. A close genetic relationship to schizophrenia has been proposed but is doubtful. Conversely, introversion has been shown to be a highly heritable personality trait. Psychological theories suggest sociocultural factors in the genesis of the disorder: In the psychodynamic approach, the SPD emerges from inadequacies in earliest relationships with parental figures. The cognitive approach suggests that the most important source of dysfunctional behaviour and affects lie in incorrect attributions that people make.

Treatment

As patients with SPD have few complaints and do not seek an interpersonal context for solving their problems, they rarely seek therapy. The disorder is most likely to come to medical attention in the course of intervention for another condition, in response to acute stressors or because of family influence. Others who come into treatment are forced to do so by family or even the legal system. Acutely stressful situations often require crisis intervention. Aims of long-term psychotherapeutic interventions are to maintain stability and support, to improve social skills and comfort, to help maximize quality of an isolated lifestyle. In treatment, clients with SPD challenge service providers with the absence of response. As they do not response to emotional leverage, therapists easily feel frustrated and ineffective. The contact between therapist and patient should be an important element of the therapy. An important step of the therapy should be to open possibilities to make new experiences and changes (Saß and Jünemann, 2001). The therapist should be aware that major changes and modifications of character structure are unlikely. The therapy should be aimed at achieving modest reductions in social isolation and in prompting more effective adjustment to new circumstances (Kalus et al. in Livesley, 1995). Behavioural psychotherapy can be helpful for some patients including, for example, methods such as problem solving, social skills training or role plays. Educational strategies may be effective in working with individuals with SPD to identify (1) their own emotions; (2) the emotions they elicit in others; and (3) possible feeling states of people with whom they relate. Intervention with individuals with SPD may include methods of cognitive therapy, e.g., exploring their self-concept and sense of where they belong in the world. Confrontation should clarify the relation of emotions to thinking and encourage these clients to be present with reality. Individual psychoanalytically oriented psychotherapies are less likely to succeed (Kalus et al. in Livesley, 1995, p.66). Most psychopharmacological interventions apply to comorbid disorders such as depression or anxiousness.

Schizotypal Personality Disorder
(partly adopted from Svenn Torgersen)

Case vignette

A 37 year old, unemployed man claimed of recurrent irrational thoughts, compulsive behaviour, and social isolation. Since his childhood he had always been eccentric, withdrawn with no real friends anxiously fearing closer relationships, preoccupied with reading stories about Dracula and other myths. He didn't share his inner thoughts or feeling with anybody, including his parents. He never finished an education, but worked in factories, often at night. Some years earlier he started doubting if his work was accurate enough. Although he recognized these thoughts as irrational, he started spending a lot of time controlling his work over and over again. Soon these compulsive controls took so much time that he could not finish his work, was continuously annoyed by intrusive vivid homosexual images, was preoccupied with doubts concerning almost everything at home and also he had to look persistently at people in order to be sure to maintain their images in his memory. He started fearing that people could notice his behaviour, and he felt that unknown people was staring at him and that they secretly were making fun of him. He complained of being unable to reveal his feelings and thoughts to other people and felt isolated. He started drinking alcohol to control his increasing anxiety. He adopted different peculiar strategies, which ended in new vicious circles of obsessive symptoms and suspiciousness.

This case is diagnosed with obsessive-compulsive disorder (OCD), Alcohol abuse and Schizotypal Personality Disorder. He had long lasting personality difficulties like suspiciousness, odd behaviour and social anxiety prior to the OCD symptoms. Comorbidity is often seen in Schizotypal Disorder, and it is the axis I disorders that usually brings the patients to treatment.

Clinical description

The historical roots of schizotypal personality disorder (STPD) are the non-psychotic personality syndromes within the spectrum of schizophrenia.

The definition of schizotypal personality disorder has remained more or less the same during the revisions of DSM and consists in DSM-IV of the following criteria:

(1) ideas of reference (excluding delusions of reference), (2) odd beliefs and magical thinking that influences behaviour and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense;" in children and adolescents, bizarre fantasies or preoccupations), (3) unusual perceptual experience, including bodily illusions, (4) odd thinking and speech (e.g., vague, circumstantial, metaphorical, over elaborate, or stereotyped), (5) suspiciousness or paranoid ideation, (6) inappropriate or constricted affects, (7) behaviour or appearance that is odd, eccentric, or peculiar, (8) lack of close friends or confidants other than first-degree relatives, (9) excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgment about self.

ICD-10 included schizotypal disorder among the psychoses and defined it partly similarly, partly differently from DSM. The only difference between DSM-IV and ICD-10 is that DSM-IV includes "ideas of reference" and "excessive social anxiety," while ICD-10 includes obsessive rumination and micropsychoses. However, ideas of reference are close to suspiciousness, and micropsychoses are close to unusual perceptual experiences, so the only real difference is social anxiety and obsessive ruminations.

Differential diagnosis

As evolving from the spectrum of schizophrenia, the boundaries between schizotypal personality disorder and schizophrenia are not easy to define. The prodromal symptoms of schizophrenia are similar to the schizotypal personality disorder. Thus, retrospectively, "premorbid" may be added to STPD, according to DSM-IV. When fully developed hallucinations and delusions are presented during a one -month period, the diagnosis is schizophrenia. However, a person with delusions or hallucinations plus negative symptoms may show a clinical picture similar to STPD; even so schizophrenia is the correct diagnosis, if the duration requirements are fulfilled. Even more difficult is the differentiation between simple schizophrenia and STPD in ICD-10. In practice, the differentiation is impossible, as the criteria for simple schizophrenia, personality changes, negative symptoms: and reduced social function is indistinguishable from the early developmental phase of STPD. However, simple schizophrenia requires change, while STPD implies no clear starting point.

The possible early start of STPD, however, may make it difficult to distinguish STPD from milder forms of pervasive developmental disorders (autism). As to other psychotic disorders, the manifestation of full-blown delusions (not only ideas of reference and suspiciousness) and hallucinations (not only illusions) preclude any diagnosis of STPD.

The boundaries between STPD and borderline personality disorder are of course difficult to draw, as both personality disorders emerged from the same borderline psychoses concept. They share the pseudo-psychotic and paranoid features, and quite a few people may live an unstable and turbulent life similar to those with borderline personality disorder. Even so, the impulsivity and affective intensity and variability in the borderline personality disorder are not part of the STPD criteria set. Furthermore, those with borderline personality disorder are not expected to display the socially inept and chronically withdrawn pattern of STPD. Instead, some people with borderline personality disorder may withdraw when they get older, as a consequence of using up the patience of their acquaintances and having experienced a brimful of disappointments in their partnerships and relationships.

STPD is close to schizoid personality disorders. The two disorders share the social isolation and the constricted affects. However, STPD has the oddness and the pseudo-psychotic features in addition. In the same vein, those with paranoid personality disorder share the paranoid features with STPD, but not the withdrawal, oddness and pseudo-psychotic features. STPD shares the social anxiety and the tendency to withdrawal with avoidant personality disorder, but not the eccentricity, paranoid features and illusions.

Comorbidity

Avoidant, paranoid and borderline personality disorders were especially highly correlated to STPD. STPD is associated with psychotic disorders including schizophrenia . Furthermore, there seems to be an association with obsessive compulsive and phobic disorders. There may also be an association with dysthymic disorder, panic disorder, somatoform disorders and eating disorders.

Prevalence

Relatively few studies of the prevalence in the general population have been performed. The samples are seldom quite representative, and differently structured interviews are applied, based on different editions of DSM. The most representative studies show a prevalence of 0.7 (Maier et al. 1992) and 0.6 (Torgersen et al. 2001). Those with a higher number of schizotypal traits have less education and more often live alone in the city centre compared

with those with a lower number. STPD seems thus more prevalent among men in clinical samples.

Diagnostic assessment

A meta-analysis of the so-called "Big-Five" and personality disorders showed that what characterized those with STPD were first and foremost Neuroticism, second Introversion and third Non-Agreeableness. The pattern was similar to paranoid and borderline personality disorders in Neuroticism and Non-agreeableness, and similar to avoidant personality disorder in Neuroticism and Introversion. Furthermore, STPD was similar to schizoid personality disorder in Introversion, to antisocial and narcissistic personality disorders in Non-agreeableness, and to dependent personality disorder in Neuroticism. There were no similarities to histrionic and obsessive-compulsive personality disorders. Together with borderline personality disorder, those with STPD were extreme on most personality disorders, three out of five dimensions.

The results of the studies of the relationships between STPD and personality dimensions fit in with the large overlap between STPD and paranoid, avoidant and borderline personality disorders. A study of the relationships between personality disorders and Cloninger's temperament and character scales suggests that STPD is negatively correlated to Self-directedness and Cooperation, and positively correlated to Self-transcendence. The results illustrate the vulnerable, withdrawn and psychotic-like aspects of STPD. Even if STPD is correlated to common personality dimensions one cannot jump to the conclusion that STPD is a construct based on these dimensions. It may be that those with schizotypal traits simply answer in an extreme way when these dimensions are measured by the questionnaires.

Then we approach the question about the categorical or dimensional nature of schizotypal features. Some statistical analyses suggest that that a latent discontinuity underlies the variation in schizotypal traits (Lenzenweger & Korfine, 1995). Others believe more in a dimensional model of schizotypy, with poorly functional individuals at one end of the dimensions, and well-functioning individuals among those with somewhat lower scores on schizotypal inventories (Goulding, 2004). Those more poorly functioning are more anhedonic and with more cognitive disturbance, while those well-functioning are more characterized by unreal experiences.

Etiology

STPD is genetically influenced as are other personality disorders (Torgersen 1986; Torgersen et al. 2000; Kendler & Hewitt, 1992). This is also the case for schizotypal traits in children (Coolidge et al. 2001). However, what is especially important is the genetic relationship to other mental disorders. Some studies suggest a familial relationship between STPD and the whole realm of psychoses (Squires-Wheeler et al. 1989; Kendler et al. 1995). As STPD evolved out of the familial schizophrenic spectrum, the genetic relationship to schizophrenia is of particular interest. Studies of co-twins of schizophrenic patients (Torgersen, 1992), and biological relatives of adopted-away schizophrenics (Kendler & Gruenberg, 1984) confirmed the specific familial and genetic relationship between STPD and schizophrenia. No other personality disorders seem to be consistently related to schizophrenia.

However, STPD as defined by DSM does not seem to cover adequately the schizophrenia-related STPD. Those adopted-away offspring of schizophrenics who develop personality disorders seem to experience frequent somatoform complaints and poor social function in

addition to withdrawal and emotional constriction (Gunderson et al. 1983). In fact, STPD consists of two syndromes that may be independently inherited (Siever, 1995; Kendler and Hewitt, 1992), a constricted/eccentric syndrome that is characterized by odd and eccentric appearance and behaviour, thoughts and communication, and a psychotic-like syndrome that is characterized by ideas of reference, magical thinking, illusions and depersonalization/derealization. While the former syndrome seems to be genetically related to schizophrenia (Torgersen, 1993), the latter is not. Even if there might exist a familial relationship between STPD and affective disorder, a genetic relationship to major depression is not confirmed.

We do not know what environmental factors influence the development of STPD. A retrospective study showed that those with STPD more often reported neglectful parenting from both parents, which means little love and also little control (Torgersen & Alnæs, 1992). Those with borderline personality disorder more often reported affectionless control, meaning little love and much control. Those with other personality disorders more often experienced affectionate constraint; much love and much control, while those without personality disorder reported optimal parenting; much love and little control.

Course and prognosis

A Norwegian twin study showed that those with STPD had poor social as well as occupational adjustment (Torgersen, 1986). Skodol et al. (2002) found dysfunction in relation to parents, sibs, and friends, occupational dysfunction, and dysfunction in relation to more distant family members among those with schizotypal personality disorder. Quality of life is also reduced among those with STPD (Cramer et al. 2003). They have a poor subjective well-being, poor self-realization, less contact with friends and family, less social support, a lot of negative life events, poor neighbourhood quality, and generally a poorer global quality than those without STPD in the general population. Among the personality disorders, nobody displayed poorer quality of life than those with STPD.

The neuropsychological and biological fundamentals of STPD are far from settled. Even so, some results are forthcoming. There seems to be a difference between the constricted/eccentric and the psychotic-like STPD syndromes. Neuro-psychological tests measuring attention and information processing observe impairment among those with constricted/eccentric traits (Siever, 1995). Indication of a low dopamine level are found among those with the constricted/eccentric syndrome, for instance by a low concentration of homovannilic acid (HVA). An adequate dopamine activity is necessary for maintenance of working memory, a function necessary for social engagement as well as other executive functions.

The deficient information processing may contribute to the social withdrawal, emotional constriction and eccentricity among those with STPD. On the other hand, those with the psychotic-like syndrome seem to have an exceptionally high level of dopamine-activity, as also demonstrated in a high concentration of HVA. The increased dopaminergic activity may explain the psychotic-like traits such as illusions, paranoid ideations etc.

Treatment

Usually psychotherapeutic approaches are applied for patients with STPD. No controlled results are published. However, from clinical experience there are some precautions that are important to take into account. Some less experienced clinicians may be fascinated with all the grotesque and symbol-rich material patients with STPD may produce. They show interest, ask for details and encourage the patient to tell more. This can be great

for the clinician, but hardly helpful for the patient. The patient may slide even more into the disturbing inner fantasies. A better approach is to dedramatize the strange thoughts and pictures, not reject, if the patient is active in telling, not refrain from showing a strong interest in the material. Instead, it is important for the patient to learn social skills, to discuss what went wrong in interpersonal situations, what behaviour is common and appropriate.

As to pharmacotherapy, the best approach is to treat the axis-I disorder in cases where those with STPD have it in addition. If the clinical picture is dominated by psychotic-like features, neuroleptic may be the treatment of choice. There are some indications that blocking of dopaminergic activation may help those with psychotic-like traits. On the other hand, those with constricted/eccentric features may be helped by drugs that functions like amphetamine - releasing dopamine and blocking its reuptake.

Paranoid Personality Disorder

(partly adopted from Elizabeth Iskander & Larry J. Siever)

Case vignette

A 36 year old divorced worker developed a severe depression after he was fired from his job and subsequently had severe alcohol problems. He presented himself to the general practitioner with somatic complaints, anxiety, compulsively washing his hands, fatigue, disturbing inner feelings of hatred towards other people. His troubles started in his childhood. He reported that he was very aggressive towards other children and he was involved in recurrent conflicts. At home he was constantly on guard. In his work relations he was involved in severe interpersonal conflicts, reacting with aggressive attacks at the slightest offences. The last years he spent working, he was continuously involved in conflicts with his colleagues. After a short contact with a female colleague who terminated the relationship with him. The only person he stayed friends with was his brother-in-law who lived a hundred kilometres away. This vignette illustrates important issues and characteristic features of the paranoid personality. First, they do not seek treatment unless they are in a crisis (fired from job) or because of additional pathology (depression). Second, when decompensated they most often get depression, panic attacks, OCD, somatoform disorder as in this case or in other cases an additional alcohol abuse. Third, the vignette may support a psychodynamic formulation of key elements in his personality functioning. His personality pathology is excessive aggression and mistrust.

Clinical Description Diagnostic Criteria ICD-10

F60.0 Paranoid personality disorder

Personality disorder characterized by:

(a) excessive sensitiveness to setbacks and rebuffs;

(b) tendency to bear grudges persistently, i.e., refusal to forgive insults and injuries or slights;

(c) suspiciousness and a pervasive tendency to distort experience by misconstruing the neutral or friendly actions of others as hostile or contemptuous;

(d) a combative and tenacious sense of personal right s out of keeping with the actual situation;

(e) recurrent suspicions, without justification, regarding sexual fidelity of spouse or sexual partner;

(f) tendency to experience excessive self-importance, manifest in a persistent self-referential attitude;

(g) preoccupation with unsubstantiated "conspiratorial" explanations of events both immediate to the patient and in the world at large.

lncludes: expansive paranoid, fanatic, querulant and sensitive paranoid personality (disorder)

Excludes: delusional disorder (F22. -) schizophrenia (F20. -)

Paranoid personality disorder is a clinically well-recognized disorder that has not, however, been the object of a great deal of investigation. Although noted in the writings of psychiatrists since the late 1800's, the condition was first called "paranoid personality" by Kraepelin in 1921 (Akhtar, 1990).

The hallmark criteria regarding paranoid personality disorder (PPD) are distrust and suspiciousness of others such that others are seen as purposefully attempting to harm one in some way without any evidence to suggest this is the case. Those with paranoid personality disorder also may be very critical of others, argumentative and rigid in beliefs, again stemming from harbouring unwarranted suspicions about people around them. This often leads to problems with relationships, both personal and in the work place.

The ICD-10 lists seven criteria (see above) of which only three must be met. The current criteria for diagnosing paranoid personality disorder in DSM IV-TR includes seven symptoms of which at least four must be met. Most are essentially the same as the ICD criteria. These include suspicion that others are harming or deceiving one in some way, preoccupation with doubts about the loyalty of friends, reluctance to confide in others out of fear that information may be used against them, reading threatening meaning into benign events, bearing grudges over insults or slights, hasty and angry reaction to perceived attacks on character, and unjustified suspicion regarding the fidelity of a spouse or partner.

There is one criterion that does not exist in the DSM IV and that is "tendency to experience excessive self-importance, manifest in a persistent self-referential attitude." This item, basically implying a level of grandiosity, also did not exist in the DSM III or III-R versions.

Differential diagnosis

Paranoid personality disorder must be diagnosed to the exclusion of schizophrenia, or any other psychotic disorder including psychosis in the context of a mood disorder. Paranoid personality disorder is considered "premorbid" if it is present prior to an Axis I psychotic disorder.

Comorbidity

There is substantial comorbidity of Axis I disorders; individuals with paranoid personality disorder appear to have an increased likelihood of developing depression, agoraphobia, obsessive compulsive disorder and alcohol or substance abuse or dependence. With regard to comorbid personality disorders, there is some variation in the literature. Generally though, it has been suggested that in clinically based samples, over 75% of patients who met paranoid personality disorder criteria also met criteria for other personality disorders, the most common were found to be schizotypal and narcissistic.

One area of research is the possible relationship of PTSD with paranoid personality disorder. When 180 outpatients were analyzed using the DSM III-R, subjects with paranoid personality disorder had a higher rate of comorbid PTSD than subjects without the disorder (29% compared with 12%) (Golier et al. 2003). In addition, they had elevated rates of physical abuse and assault in childhood and adulthood (54% compared with 35%). This suggests a possible link between trauma during early events in life and subsequent paranoid behaviour and mistrust.

Another area that has received some attention is the relationship of violence to paranoid personality disorder. Paranoid cognitive personality style was found to increase the risk of violence in subjects with personality disorders, particularly schizophrenia spectrum disorders (Nestor, 2002).

Prevalence

According to the DSM-IV, the prevalence of paranoid personality disorder was 0.5 to 2.5% in the general public, and more common in males. Interestingly, the 1997 National Survey of Mental Health and Wellbeing (conducted in Australia) using the ICD-10 to assess personality disorders found a 1.34 % prevalence of paranoid personality disorder and no sex difference, despite the similarities in criteria between the DSM and the ICD.

There is some current evidence that paranoid personality disorder may be more difficult to diagnose than other personality disorders. A study of interrater reliability using DSM IV achieved good agreement. However, in the same study, when analyzing test-retest reliability based on how consistent a patient's report is from one clinician to another, and how information is interpreted and scored, paranoid personality disorder had the lowest reliability of all the personality disorders (Zanarini et al. 2000).

Etiology

It has been suggested that paranoid personality disorder may be related to certain Axis I disorders, including schizophrenia and delusional disorder. Kendler found a much higher risk of paranoid personality disorder in first degree relatives of those with delusional disorder as opposed to relatives of those with schizophrenia, 4.8% compared to 0.8% (Kendler et al. 1985).

On the other hand, paranoid personality disorder was significantly more common in the biologic relatives of patients with schizophrenia when compared with relatives of controls (Kendler et al. 1982).

Using data from the Roscommon family study, an epidemiologic study conducted in Ireland, it was discovered that biological relatives of those with schizophrenia had a significantly higher amount of paranoid personality disorder compared with relatives of controls (Kendler et al. 1993).

As with other disorders, cultural factors must be taken into account in diagnosing this disorder. There are some groups that might, for reasons of maltreatment, language barriers, and unfamiliarity to this society, display what could be labelled paranoid traits. Those groups include: minority groups, immigrants and refugees. In an epidemiologic study recently completed on personality disorders, minorities such as blacks, Hispanics and Native Americans were at greater risk for having paranoid personality disorder than whites (Grant et al. 2004). Also according to the same study, paranoid personality disorder was more

common among younger people (18-29), those with lower incomes, and those who were divorced or never married. Some of these findings are not surprising, taking into account the nature of paranoid personality disorder. However, this does bring up the question of which came first: Are some paranoid traits the result of maltreatment by others due to socioeconomic status, race, etc., or does the disorder contribute to, for example, inability to succeed professionally or remain in a relationship? There appears to be a combination of both, which can contribute to complications in diagnosing the disorder.

Course and Prognosis

Paranoid personality disorder can be noted first in childhood; symptoms observed include solitariness, social anxiety and odd thoughts and language. There is not a lot of data regarding the course and prognosis of the disorder. This is likely due to the fact that as it is a personality disorder, it tends to be stable over adult life and although it can cause interpersonal problems, does not often require treatment. It has been observed that the course of the disorder rarely worsens or goes into remission (Akhtar, 1990).

Treatment

There is no specific treatment or medication for paranoid personality disorder. When existing in conjunction with other personality disorders, i.e., borderline personality disorder, treatment may be sought but that is primarily due to symptoms experienced in other personality disorders. There is some data on the effectiveness of day treatments for patients with personality disorders in general (Karterud et al. 2003). Treatment results, although effective for some personality disorders (i.e., borderline), were the poorest for those with paranoid, schizoid, and schizotypal personality disorders.

Cluster B

Cluster B includes four personality disorders: Antisocial (ASPD), Borderline (BPD), Histrionic (HPD) and Narcissistic (NPD). According to DSM IV-TR individuals with these disorders appear dramatic, emotional or erratic.

For additional information and references see Module II in Simonsen E, Ronningstam E, Millon T (Eds). (2007). WPA ISSPD Educational Program on Personality Disorders. www.wpanet.org/education/education.shtml: Hart S., Cooke D. Antisocial Personality Disorder (pp. 60-66); Bateman A., Fonagy P. Borderline Personality Disorder (pp. 74-83); Pfohl B. Histrionic Personality Disorder (pp. 90-94) and Ronningstam E: Narcissistic Personality Disorder (pp.95-103).

Antisocial Personality Disorder

(adopted from Stephen Hart & David Cooke)

Case vignette

This is a 27 year old male who committed murder at age 17. He stayed in a high-security hospital for 10 years and started individual treatment after being released. He was an intelligent boy who did well in school until his peers began to tease him. This made him feel

helpless and unable to defend himself. At home, however, he felt strong and supportive of his mother. His father lived with another woman. He experienced him self as a looser among his pears but as a winner with his mother. At the end of primary school his father, who then had accumulated substantial wealth, returned home, and the parents resumed their marriage and intimacy. His situation at school changed as he became popular and the teasing stopped, but he still felt insecure and uneasy. He decided to attend karate school to gain a sense of power. A peer introduced him to the criminal milieu where he felt accepted and appreciated. During a robbery he became incredible angry and physically violent without really understanding why. The victim died as a consequence of his attack. He was send to prison for 2 years, followed by a high security hospital for treatment. While he accepted his prison sentence he protested treatment in psychiatric hospital. He was suspicious, remained non-relative and was often restrained due to anger outbursts. A therapist confronted him with the fact that his behaviour could lead to prolonged hospital stay and pointed to his choice of future inside or outside the hospital. This was turning point that made him focus on goals and training for a future out in real life. After discharge he continued to work on self-esteem and trustworthiness, shame and guilt and how to understand, control and come to terms with his anger. Two years later he was married with a son, and pursued a career as a teacher.

Clinical description

Diagnostic Criteria ICD-10

F60.2 Dissocial personality disorder

Personality disorder, usually coming to attention because of a gross disparity between behaviour and the prevailing social norms, and characterized by:

(a) callous unconcern for the feelings of others;

(b) gross and persistent attitude of irresponsibility and disregard for social norms, rules and obligations;

(c) incapacity to maintain enduring relationships, though having no difficulty in establishing them;

(d) very low tolerance to frustration and a low threshold for discharge of aggression, including violence;

(e) incapacity to experience guilt or to profit from experience, particularly punishment;

(f) marked proneness to blame others, or to offer plausible rationalizations, for the behaviour that has brought the patient into conflict with society.

There may also be persistent irritability as an associated feature. Conduct disorder during childhood and adolescence, though not invariably present, may further support the diagnosis.

Includes: amoral, antisocial, asocial, psychopathic, and sociopathic personality (disorder)

Excludes: conduct disorders (F91. -) emotionally unstable personality disorder (F60.3)

People with ASPD (Dissocial in ICD 10) show unreliability, recklessness, restlessness, disruptiveness, and aggressiveness. According to DSM IV-TR (2000) they have a pervasive pattern of disregard for, and violation of, the rights of others. Negative symptoms include lack of anxiety and remorse, and lack of emotional depth and stability. They are interpersonally

detached, suspicious, and exploitative, and they lack commitment to and concern for others. Antagonism, deceitfulness, manipulativeness, dishonesty, and glibness are typical interpersonal features. Some come across as self-aggrandizing and self-justifying with a sense of entitlement and invulnerability. Cognitive deficits include inflexibility, and lack of concentration.

Prevalence

The lifetime prevalence of ASPD is about 2-3 % in the general population. The rate in the community and psychiatric population is relatively low (1-2%), but among correctional offenders, forensic psychiatric patients, and substance users it is high (< 50%).

Etiology

Theoretical models for the etiology of ASPD suggest a mental abnormality with social and biological causal factors, and have excluded child rearing experiences, familial dysfunctions, or adverse life experiences. Sociocultural and neurological factors are associated with symptoms of ASPD, but not clearly pathognomonic. Other theories consider ASPD as an extreme variant of personality traits found in all people, or as an adaptation. Early manifestations of ASPD are evident in children (age 6-10 years), and it is common that adults with ASPD in their childhood or adolescence were diagnosed with conduct disorder, oppositional defiant disorder, or attention deficit hyperactivity disorder.

Course

Symptoms of ASPD can persist into middle or late adulthood. ASPD has been associated with increased rate of morbidity and mortality.

Comorbidity

Antisocial personality disorder is often comorbid with substance-use disorders, but also with other personality disorders, such as the Cluster B borderline, narcissistic, and histrionic in DSM-IV or emotionally unstable and histrionic in ICD-10.

Treatment

There is no good evidence that ASPD can be successfully treated. Most treatment studies have aimed at reducing criminal behaviour in mixed groups of patients or offenders, including some with ASPD, rather than attempting to alleviate symptoms of ASPD. Nevertheless, structured psychosocial treatments that focus on the acquisition of important life skills, such as communication, assertiveness, and anger management skills are useful (Hemphill & Hart, 2002). Pharmacological treatments that target treatment-interfering symptoms, such as extreme hostility or impulsivity, may play a useful adjunctive role in certain cases.

Borderline personality disorder

(adopted from Anthony Bateman & Peter Fonagy)

Case vignette

A 23 years old woman reacted with depressive symptoms and suicidal thoughts to the death of her grandfather. She was treated with antidepressant medication without addressing the

loss. Three years later after a suicidal attempt, she was admitted to hospital where she first presented with depressed mood and suicidal thoughts, but quickly engaged in vivid conversations with the others patients. She was discharged with the diagnosis of personality disorder, but soon re-admitted because of suicidal thoughts, and referred to an outpatient program specialized on treatment of personality disorder. Since childhood she had unstable mood, aggressive temperament and self-destructive behaviour (head banging). At the age of 10 she was sexually abused by an older man. Suicidal thoughts and urges to kill herself was first experienced at age 11. Since age 13 she has had multiple sexual partners but also one 7 year long relationship which was quite unstable with frequent conflicts and impulsive acts. She dropped out of school and has been living on sickness benefits, interrupted by short periods of unskilled employment. In a two year psychoanalytic treatment program with one individual session and one group session a week in addition to psycho education, she worked together with other patients on identifying and understanding the characteristic features of BPD, and the dynamics of borderline pathology with a special focus on self-destructive behaviour. Her self-destructive behaviour tapered off after 3 months as she began to process her feelings of aggression and sadness. The pharmacological treatment terminated after 6 months and she quickly became less sedated and anxious. She resumed school towards the end of the first year of treatment, with the intention of taking a degree in teaching. The relationship with her boyfriend stabilized. Contacts with class became more satisfying, and conflicts with her teachers stopped. Her ability to begin to contain feelings increased dramatically.

Clinical Description

Diagnostic Criteria ICD-10

F60.3 Emotionally unstable personality disorder

A personality disorder in which there is a marked tendency to act impulsively without consideration of the consequences, together with affective instability. The ability to plan ahead may be minimal, and outbursts of intense anger may often lead to violence or "behavioural explosions"; these are easily precipitated when impulsive acts are criticized or thwarted by others. Two variants of this personality disorder are specified, and both share this general theme of impulsiveness and lack of self-control.

- F60.30 Impulsive type

The predominant characteristics are emotional instability and lack of impulse control. Outbursts of violence or threatening behaviour are common, particularly in response to criticism by others.

lncludes: explosive and aggressive personality (disorder) Excludes: dissocial personality disorder (F60.2)

- F60.31 Borderline type

Several of the characteristics of emotional instability are present; in addition, the patient's own self-image, aims, and internal preferences (including sexual) are often unclear or disturbed. There are usually chronic feelings of emptiness. A liability to become involved in intense and unstable relations hip s may cause repeated emotional crises and may be associated with excessive efforts to avoid abandonment and a series of suicidal threats or acts of self-harm (although these may occur without obvious precipitants)

lncludes: borderline personality (disorder)

Individuals with BPD (Emotionally unstable in ICD 10) have according to DSM IV-TR (2000) a pervasive pattern of instability in interpersonal relationships, self-image and affects, and marked impulsivity. They show frantic efforts to avoid real or imagined abandonment, a pattern of unstable and intense interpersonal relationships and identity disturbance. They also present with impulsivity, recurrent suicidal gestures, affective instability, chronic feelings of emptiness, inappropriate intense anger. In severe cases transient stress-related paranoid ideation or severe dissociative symptoms are noticeable.

Prevalence

BPD is relatively rare in the general population (0.2%- 1.8%) while prevalence rate among psychiatric inpatient and outpatient is higher (15% – 25%).

Etiology

Early separations and losses, disturbed parental involvement with conflictual relationships, childhood history of physical and/or sexual abuse, and high prevalence of affective disorder in first-degree relatives of borderline probands are specific developmental and psychosocial factors for BPD (Zanarini & Frankenburg, 1997). Low level of serotonin, stress sensitivity and a tendency for impulsive aggression can, when combined with psychosocial factors, contribute to adult BPD.

Course

Although borderline patients improve over time they still can remain functionally impaired. Especially those who experienced sexual abuse or incest in childhood have a poor prognosis. Emotional instability, impulsivity and aggressive relationships worsen prognosis as do comorbid substance abuse, and schizotypal, antisocial or paranoid features.

Comorbidity

Around 60% of patients with BPD have major depressive disorder, 30% panic disorder with agoraphobia, 12% substance use disorder, 10% bipolar-I, and 4% bipolar-II disorder. Comorbid BPD tends to interfere with treatment of Axis I.

Treatment

Multimodal treatment and a combination of psychotherapy and psychopharmacological treatment offer the best chance of a good outcome (Oldham, Phillips, Gabbard, et al. 2001). Psychodynamic treatment is preferable while long in-patient treatment has proved ineffective. Evidence based manualized treatment modalities, i.e., Mentalization Based Treatment (Bateman & Fonagy, 1999; Bateman & Fonagy, 2001), Cognitive therapy (Ryle, 1997), Dialectic Behaviour Therapy (DBT) (Lenihan 1993; Linehan Heard, Armstrong, 1993) and Transference Focused Psychotherapy (TFP) (Clarkin, Foelsch, Levy, et al., 2001), have all proved beneficial and effective in changing borderline symptoms and character functioning. Although no specific psychotropic drug is effective for BPD, some can help reducing disabling symptoms; i.e., typical and atypical antipsychotic drugs, tricyclic antidepressants (TCA's) and selective serotonin reuptake inhibitors (SSRI's), monoamine oxidase inhibitors (MAOI's), and mood stabilisers.

Narcissistic personality disorder

Case vignette

A 42-year-old male professional in public office, was forced to resign after being arrested when visiting a brothel. In the aftermath he suffered from depression and considerable alcohol consumption, and was admitted for a three months treatment. He stopped drinking, but his depression remained nonresponsive to anti-depressant medication. Still without meaningful activities he felt empty and restless, and he was referred to psychotherapy. Developmental history indicates that at age 5 his father left the family, and they did not meet until he was in law school. He was always ahead of his age and went through school without difficulty. In law school he got high marks without hard work. He had many acquaintances but no friends, and he felt like an outsider. He got married and had two children. Reaching mid-thirties he felt bored. He had everything: house, career, and family. He was respected and accomplished, but felt he didn't belong. He started drinking heavily and visiting brothels. The psychotherapist found him self-assured, easily irritated, and quick to make devaluating remarks, and felt a mixture of irritation, compassion and powerlessness. Interactions during weekly appointments were extremely difficult. Unwilling to explore his situation or his feelings, he blamed the therapist for the impasse and told him that he will not change and that the therapist could not help. The therapist dreaded the appointments, while the patient despite finding the sessions unhelpful, always showed up. When the therapist announced a three weeks break his patient suggested the treatment to end and did not return. Nine months later he informed the therapist that he moved to another city, had a leading position working with international trade, and was greeted as a king. He said nothing about his wife and children. Nor did he indicate how he felt about the treatment.

Clinical Description

People with NPD (not included in the ICD 10) have a grandiose sense of self-importance and accompanying grandiose fantasies. According to DSM-IV TR (2000) they present a pervasive pattern of grandiosity, need for admiration and lack of empathy. In addition they have a sense of entitlement and tendencies to be exploitive, and take advantage of other people. They can come across as arrogant and haughty or boastful and self-centered. However, they also have vulnerable and fluctuating self-esteem, feelings of shame, intense reactions to criticism or defeat, and vocational irregularities. Some may appear more sensitive, inhibited, vulnerable, shame-ridden and socially withdrawn, and others can present with psychopathic or antisocial characteristics.

Prevalence

Variable prevalence rate of NPD has been found both in the general community (1% - 6%) (Stinson, Dawson Goldstein et al 2008) and in the clinical population (1.3% - 17%).

Etiology

Studies have suggested a genetic influence on the development of NPD, including hypersensitivity, strong aggressive drive, low anxiety or frustration tolerance, and defects in affect regulation (Torgersen et al 2000; Schore, 1994). Inconsistent attunement and insufficient attachment in the early parent-child interaction can lead to failure in the development of self-esteem and affect regulation.

Course and prognosis

Although narcissistic traits can be frequent in adolescence, NPD develop in adulthood and can persist into old age. Severe disability has been indicated especially among those with comorbid Axis I disorder. NPD patients with ability for object relations actually improve over time and may have better prognosis (Ronningstam, Gunderson, Lyons 1995).

Comorbidity

NPD is considered to have one of the highest rates of diagnostic overlap among the Axis II disorders, especially with ASPD (25%). Major depression and dysthymia are the most common concomitant Axis I disorders (42 - 50%), followed by substance use disorder (24 – 50%) and bipolar disorder (5 – 11 %). Co-occurring narcissistic features can worsen course and prognosis for Axis I disorders.

Treatment

Psychoanalysis and psychoanalytically oriented psychotherapy are the most common treatment for NPD (Kernberg, 1975; Kohut, 1968; Fiscalini, 1994). Additional modalities include the Schema Focused Therapy (Young & Flanagan, 1998), and couples or family therapy (Solomon, 1998; Kirshner, 2001). Potentially beneficial psychopharmacological treatment focused on mood, anger or anxiety, is often challenged by the patients' reluctance to adhere to such modality.

Histrionic Personality Disorder

(adopted from Bruce Pfohl)

Case vignette

A 25-year-old female university student sought psychoanalytic treatment as she suffered from depression, difficulties in interpersonal relationships, and vocational dissatisfaction. Her first panic attack occurred during the last year in high school when her boyfriend was treated for panic attacks. She believed she was "influenced" by him. In psychotherapy she overcame family difficulties, especially in relation to her mother, but continued to feel insecure and pessimistic, blaming it all on her boyfriend. Their conflictual relationship ended when she had an episode of depression. She felt she wanted to die and sought consultation for psychoanalytic treatment saying that she was wasting her life, and lacked motivation for studies or career. She dreamt about her former boyfriend, and after breaking up with two other men she felt extremely lonely. She is the third of seven children. The father was hard-working, affectionate and caring, but also irritable and depressive. The mother was impulsive and sarcastic. Mother and daughter had a close but conflictive relationship as the mother could be intrusive, opinionated and idealizing. At age three the parents moved abroad for one year and left her to live with relatives. Upon their return she was presented to a baby brother. Significant sensitivity during her school years led her to break up friendships and feel extremely lonely. She did well at university, formed friendships but noticed that she often felt rejected without knowing why. In psychoanalysis four times per week she presented several contradictions, i.e., pursuing treatment and lapsing, or describing her mother as unsupportive, cold and envious but nevertheless readily resorting to her when facing difficulties. As the psychoanalysis progressed she presented infantile histrionic

features; a precarious identity, strong affective dependence, dissociation, infantilization and self destructive work related behaviour. She brought multiple dreams to the sessions and gave vivid images of conflicts that worried her. Despite efforts to interpret, the analyst noticed no progress. Paradoxically, her presentation of dreams and associations indicated in-depth psychological work, but her persistent tardiness and absenteeism reflected the opposite. After eight months of psychoanalysis, the analyst suggested 3 sessions per week of face to face psychotherapy and referred her to a colleague.

Clinical description

Diagnostic Criteria DSM-10

F60.4 Histrionic personality disorder

Personality disorder characterized by:

(a) self-dramatization, theatricality, exaggerated expression of emotions;

(b) suggestibility, easily influenced by others or by circumstances;

(c) shallow and labile affectivity;

(d) continual seeking for excitement and activities in which the patient is the centre of attention;

(e) inappropriate seductiveness in appearance or behaviour;

(f) over-concern with physical attractiveness

Associated features may include egocentricity, self-indulgence, continuous longing for appreciation, feelings that are easily hurt, and persistent manipulative behaviour to achieve own needs.

lncludes: hysterical and psychoinfantile personality (disorder)

In DSM-IV-TR (2000) HPD is described as a pervasive pattern of excessive emotionality and attention-seeking behaviour. People with HPD show seductive inappropriate behaviour, shallow emotional expressions, impressionistic speech, suggestibility, and a belief that relationships are more intimate than they really are. They have strong need for attention, pursued by a sensational physical appearance, or by being emotionally dramatic and expressive, or inappropriately sexually provocative or seductive. Individuals with HPD range from high level classical hysterical character neuroses to more primitive character functioning presenting with dissociative language, vivid fantasy life and infantile dependence.

Prevalence

DSM-IV-TR (2000) suggests that about 2% - 3% of the general population and 5% – 10% of the clinical population meet criteria for HPD.

Etiology

Repression and somatisation of strong emotions are considered the main etiological factors in hysteria.

Course and prognosis

The course and prognosis of HPD depends upon comorbidity and level of severity of the disorder. Intense and chronic anger and stormy close relationships are indicators of poorer prognosis. Ability to reflect and tolerate regularity can prevent treatment failure (Stone, 2005).

Comorbidity

Major depressive disorder, Somatization disorder and Conversion disorder are the most common comorbid Axis I disorder with HPD. Association between the other Cluster B personality disorders have also been found. Individuals with HPD can also present with increased attention driven risk for suicidal gestures and threats.

Treatment

Histrionic personality traits are usually requiring long-tem treatment and psychodynamic psychotherapy is the most common modality. Higher functioning neurotically organized individuals can be treated with psychoanalysis, while people with more primitive functioning may benefit from supportive or cognitive therapy which focuses on the patient's automatic thoughts and beliefs and on modifying emotional and interpersonal reactivity (Gabbard & Allison, 2007).

Cluster C

Cluster C includes the Avoidant, Dependent, and Obsessive-Compulsive Personality Disorders. Individuals with these disorders often appear anxious or fearful. Avoidant Personality Disorders exhibit a pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation. Dependent Personality Disorders show a pattern of submissive and clinging behavior that evidence an excessive need to be taken care of. Lastly, Obsessive-Compulsive Personality Disorders manifest a preoccupation with orderliness, perfectionism, and control.

For additional information and references see Module II in Simonsen E, Ronningstam E, Millon T (Eds). (2007). WPA ISSPD Educational Program on Personality Disorders. www.wpanet.org/education/education.shtml:

Avoidant Personality Disorder

Case Vignette

The patient was a 35 year old, unmarried data technician referred to a specialized treatment program for personality disorders from an out-patient drug addiction service. His personality pathology was considered more devastating than his substance abuse. Presenting complaints included low self esteem, loneliness, sense of emptiness, suicidal ideation, social isolation, substance abuse, general dissatisfaction with life. Present complaints had been chronic in nature, dating back to childhood. He recalled having daily suicidal thoughts for several years in his early youth. On axis I he fulfilled the criteria for dysthymic disorder and drug abuse in partial remission, but not panic disorder or social phobia. His avoidant behavior was more prominent than his level of experienced anxiety. On axis II he fulfilled all seven criteria for avoidant personality disorder and an additional seven criteria spread across other

personality disorders. The most prominent feature was a pervasive fear of being ridiculed when interacting with others. In a group-based treatment program lasting for 20 weeks, he was a regular, but somewhat detached participant. The therapists encountered a series of problems related to passivity: He postponed most of his obligations, resisted sorting out practical affairs, did not pay his bills and avoided contacting people who could be helpful.

Clinical description

Diagnostic Criteria ICD-10

F60.6 Anxious [avoidant] personality disorder

Personality disorder characterized by:

(a) persistent and pervasive feelings of tension and apprehension;

(b) belief that one is socially inept, personally unappealing, or inferior to others;

(c) excessive preoccupation with being criticized or rejected in social situations;

(d) unwillingness to become involved with people unless certain of being liked;

(e) restrictions in lifestyle because of need to have physical security;

(f) avoidance of social or occupational activities that involve significant interpersonal contact because of fear of criticism, disapproval, or rejection.

Associated features may include hypersensitivity to rejection and criticism

Avoidant personality disorder is a pervasive pattern of social inhibition, feelings of inadequacy or inferiority, and hypersensitivity to negative evaluation, according the definition of American Psychiatric Association DSM-IV-TR (American Psychiatric Association, 2000). The term of avoidant personality disorder has been used in DSM, while anxious personality disorder is used in ICD-10 (World Health Organization, 1993). Although the term avoidant personality disorder was first used by Millon, (1969) these patients have been described as sensitive character (Kretschmer, 1921), introvert (Jung, 1936), interpersonally avoidant (Horney, 1945)), insecure psychopath (Schneider, 1950), phobic personalities (Fenichel, 1945), or active-detached personalities (Millon, 1973). People with this disorder are timid, extremely self-conscious and fearful of criticism, humiliation, and rejection.

Comorbidity

Clinical literature has reported that Cluster C personality disorders including avoidant personality disorder often co-occur with mood and anxiety disorders. Avoidant and dependent personality disorders were strongly related to mood disorders, especially major depression, dysthymia, and mania. Avoidant personality disorders were reported to be strongly related to anxiety disorders, especially panic disorder with agoraphobia and social phobia. In addition to mood and anxiety disorders, eating disorders tend to be comorbid with avoidant personality disorder (Oldham et al. 1995). Avoidant personality disorder often co-occurs with other Cluster C personality disorders. This disorder is especially strongly correlated with dependent personality disorder.

Prevalence

Although there was concern that the prevalence of avoidant personality disorder might be low when it was first included in the DSMIII classification system, it became clear that this

is one of most common personality disorders. However, this disorder appears to be more prevalent according to the recent national studies with a large sample size e.g., 2-2.5%. It is quite prevalent within clinical settings and reported to present 5% -35% in psychiatric populations (Mattia et al. 2001). The odds of avoidant personality disorder are greater for the lower income group, people with less than a high school education, the widowed/divorced /separated and never married, and residents in the most urbanized areas (Grant et al., 2004).

Etiology

Although the etiology of avoidant personality disorder is not known, a few models are proposed. The biological learning theory hypothesizes that the interaction of a biologically determined sensitivity to interpersonal relationships and social experiences affects the development of the disorder. It is also postulated to be an extreme variant of the personality traits of introversion and neuroticism which have heritability. According to the interpersonal etiology model, the disorder is explained based on a conflict between seeking closeness and fearing it. Cognitive theory hypothesizes negative schema which originate in early childhood, and which lead to social avoidance behavior. When the disorder begins in childhood, the symptoms could worsen in adolescence due to the complex and demanding social relationships of this time.

Treatment

It is essential to establish a good therapeutic relationship which is, however, very difficult because of the patients' low self-esteem and hypersensitivity to rejection. Cognitive individual or group format is effective for these types of patients. Social skills training, systematic desensitization, and graded hierarchy of in vivo exposure to feared social situations could be useful (Beck & Freeman, 1990). Both short-term dynamic psychotherapy and cognitive therapy have a place in the treatment of patients with cluster C personality disorders (Svartberg et al. 2004). Exploratory and supportive group therapy may be helpful for these patients by providing a holding environment in which they can share their insecure feelings.

Dependent Personality Disorder

Case Vignette

The patient was a 27 year old white female administrative assistant whose work required much use of the computer and data entry. She gradually began to develop pain in her wrists. Physicians diagnosed a potential carpal tunnel syndrome. The damage to her wrists was not reparable by surgery and Sally was left in significant daily pain. The patient demonstrates the key aspect of Dependent personality, the need to please others even at the expense to herself. The degree to which her self-destructive passivity and compliance at work stemmed from her early experiences within the family are unclear, but her parents' overprotectiveness likely played some role in the etiology of her personality pathology. Research confirms that overprotective and authoritarian parenting, alone or in combination, often lead to excessive interpersonal dependency in offspring.

Clinical description

Diagnostic Criteria ICD-10

F60.7 Dependent personality disorder

Personality disorder characterized by:

(a) encouraging or allowing others to make most of one's important life decisions;

(b) subordination of one's own needs to those of others on whom one is dependent, and undue compliance with their wishes;

(c) unwillingness to make even reasonable demands on the people one depends on;

(d) feeling uncomfortable or helpless when alone, because of exaggerated fears of inability to care for oneself;

(e) preoccupation with fears of being abandoned by a person with whom one has a close relationship, and of being left to care for oneself;

(f) limited capacity to make everyday decisions without an excessive amount of advice and reassurance from others.

Associated features may include perceiving oneself as helpless, incompetent, and lacking stamina

lncludes: asthenic, inadequate, passive, and self-defeating personality (disorder)

Although early diagnosticians discussed at length the clinical implications of exaggerated dependency needs, it was not until publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) that dependent personality disorder (DPD) became a full-fledged diagnostic category. DPD is defined as "a pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation" (APA, 1994, p. 668). The person must show several of the following symptoms to receive a DPD diagnosis: difficulty making everyday decisions without excessive advice and reassurance; needing others to assume responsibility for most major areas of life; difficulty initiating projects or doing things on one's own; going to excessive lengths to obtain nurturance and support; feeling uncomfortable and helpless when alone, being unrealistically preoccupied with fears of being left to care for oneself.

Comorbidity

The DSM-IV-TR indicates that three Axis I diagnoses - mood disorders, anxiety disorders, and adjustment disorder - show substantial comorbidity with DPD. Evidence supports continued inclusion of these three categories in future versions of the DSM, but also suggests that eating disorders and somatisation disorder co-occur with DPD at higher-than-expected rates (Piper et al. 2001).

Prevalence

Problematic dependency is widespread in the community as well as in clinical populations, and is associated with an array of psychological disorders. Studies typically report Dependent Personality Disorder prevalence rates of between 15 % and 25% in hospital and rehabilitation settings (Oldham et al. 1995). Bornstein's (1993, 1997) meta-analyses of epidemiological findings indicated that gender moderates DPD prevalence rates. When data from extant studies were combined, the overall base rate of DPD was 11% in women and 8% in men. Although this difference seems modest, it is highly significant.

Etiology

Several theoretical frameworks have been particularly influential in conceptualizing the etiology of the Dependent Personality. Research does not support the early psychodynamic hypothesis that variations in infantile feeding and weaning behaviors play a role in the development of dependent personality traits (Bornstein, 1996). Many psychodynamic researchers (e.g., Luborsky & Crits-Christoph, 1990) now conceptualize problematic dependency as resulting from unconscious conflicts. Cognitive models of DPD focus on the ways in which a person's manner of thinking helps foster dependent behavior. As Freeman and Leaf (1989) noted, dependency-related automatic thoughts (i.e., reflexive self-statements that reflect the person's perceived lack of competence) are central in this process. Automatic thoughts are accompanied by negative self statements, which combine to create a persistent attributional bias that reinforces the person's view of himself as vulnerable and weak. A vicious cycle ensues.

Treatment

No studies have documented the long-term course of DPD in inpatients, outpatients, or community adults. In the short term, research confirms that dependent patients exhibit behaviors that both facilitate and undermine treatment. For example, dependent psychotherapy patients are cooperative and conscientious, but also make more requests for after-hours contact. Dependent patients delay less long than nondependent patients when psychological symptoms appear, but they also have difficulty terminating treatment after symptoms remit (Bornstein, 1993). Over the years clinicians have provided recommendations for intervention strategies based on cognitive (Young, 1994), psychodynamic (Luborsky & Crits-Christoph, 1990), behavioral (Turkat, 1990), and experiential (Schneider & May, 1995) treatment models. However, only two studies assessed changes in DPD symptoms during the course of psychotherapy, and these investigations produced conflicting results.

Obsessive-Compulsive Personality Disorder

Case Vignette

The patient was a 42-year-old single male, who lives with his parents. He has been unemployed for some time. He presented to the anxiety disorders clinic at a major teaching hospital, because of concerns regarding his long-term unemployment. He tended to procrastinate when making decisions or carrying out plans. On weekends, when the family planned to visit the grandparents he would start packing on Friday afternoon, but on many occasions did not finish the packing until Sunday, by which time it was too late to go. He spent long periods of time in the bathroom, would take half an hour to wash his hands-first washing the tap, then his hands, then the tap again. This routine also made it difficult for him to go out and look for job. In fact, it totally prevented him from doing so. After leaving school, he has had 30 or 40 jobs, mostly factory work. The longest he has lasted in a job has been one week, often only one day. He was very punctual in treatment and never missed a session; he talked freely, and in great detail. The initial part of therapy mainly dealt with family relationships. When the time came to leave the sessions he would often continue talking and delaying even when the therapist was standing at the door.

Clinical Descriptions

Diagnostic Criteria ICD-10

F60.5 Anankastic personality disorder

Personality disorder characterized by:

(a) feelings of excessive doubt and caution;

(b) preoccupation with details, rules, lists , order, organization or schedule;

(c) perfectionism that interferes with task completion;

(d) excessive conscientiousness, scrupulousness, and undue preoccupation with productivity to the exclusion of pleasure and interpersonal relationships;

(e) excessive pedantry and adherence to social conventions;

(f) rigidity and stubbornness;

(g) unreasonable insistence by the patient that others submit to exactly his or her way of doing things, or unreas6nable reluctance to allow others to do things;

(h) intrusion of insistent and unwelcome thoughts or impulses.

lncludes: compulsive and obsessional personality (disorder) obsessive - compulsive personality disorder

Excludes: obsessive - compulsive disorder (F42. -)

Diagnostic criteria of ICD-10 (WHO, 1992) and DSM-IV-TR (APA, 2000) for the OCPD (or anankastic personality disorder, following the ICD-10) are quite similar. Both nosological systems describe a syndrome characterized by symptoms such as excessive perfectionism, stubbornness, rigidity, and lack of decision. For the DSM-IV-TR, the OCPD is a pervasive pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency, beginning by early adulthood and present in a variety of contexts.

Comorbidity

Most research shows that most individuals with Axis I Obsessive-Compulsive Disorder do not fulfill the criteria of OCPD. Furthermore, it has been found that patients with OCD and with a personality disorder show similar or more frequent relationships with the avoidant or dependent personality disorder than with OCPD. Comorbidity with other personality disorders has varied markedly depending on the specific study.

Prevalence

(Maier et al. (1992) found that the Obsessive-Compulsive Personality Disorder was the second most frequent personality disorder (among the 11 included in the DSM-III-R) in his study sample (individuals without psychiatric disorders), showing a range from 1.6% to 6.4%, while the prevalence found by Widiger & Sanderson (1997) ranged from 1% to 3%.

Etiology

The etiology of Obsessive-Compulsive Personality Disorder is unknown. There are not data regarding the influence of biological factors in the onset and development of this disorder, but it is believed that environmental factors play an important role in its etiology. Millon (1996)

proposes some of these tentative variables: parental over-control is a method of restrictive child-rearing in which punitive processes are used to set distinct limits on children's behavior. As long as they operate within the parental approved boundaries, children are safe from parental punishment. The acquisition of behavior patterns of OCPD are learned vicariously and by imitation.

Treatment

Neither pharmacological, nor psychoanalytical, interpersonal, or cognitive-behavioral perspectives have empirical proven techniques for the modification of OCPD. One of the most frequent symptoms present in individuals with OCPD, causing inefficiency is their inability to give priority to important tasks instead of focusing on trivial or less important tasks, and also their inefficient distribution of time. A coping strategy would be good management of time strategies. Furthermore, these strategies would allow the individual to save time and devote it to other leisure and social activities.

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7.3.10 Cluster C

7.3.11 Curriculum Suggestions

The following general questions are suggested to be discussed in classrooms:

1. Why are PDs useful for mental health workers (psychiatrists, psychologists, social workers) to understand as a key component of their clinical activities?
2. Discuss the social costs of the PDs, their widespread prevalence and their associated civic and public health consequences and disruptions.
3. Why is the traditional concept of "disease" not suitable when discussing the nature of the PDs? Why do some thinkers consider PDs to be best considered as similar to the biological immune system?
4. How can normality and abnormality best be differentiated? Is there a sharp line separating them or are they on a continuum?
5. The history of ideas about personality goes back to the early Greeks. Discuss some of these interesting ideas and major thinkers from the past to the present.
6. What are some of the issues, as well as the similarities and differences between the ICD-10 and DSM-IV in their formulation of the PDs.
7. Do personality disorders really exist or are they just convenient fictions of theory, clinical observation or research investigations?
8. What are the issues in the categorical vs. dimensional PD debate, and does the prototypical idea help solve them?
9. Discuss the role of biogenic, psychogenic and sociogenic influences in PD development pathogenesis? Describe some of the research evidence for their respective contributions.
10. Describe the several modes and specific tools of diagnosing the PDs, and discuss their respective strengths and weaknesses.
11. Go into considerable detail in specifying the strengths of either the cognitive or the psychodynamic approach to therapy for the PDs.
12. What are the comparative advantages and disadvantages of adhering to one specific school of therapy versus several combined schools, e.g., behavioural, pharmacologic in treating the PDs.

Curriculum Suggestions – Module II

The following questions for each personality disorder are suggested to be discussed in classrooms:

1. What are the most outstanding and significant features for each personality disorder that best identifies and differentiates them from other personality disorders?
2. In what way does each personality disorder resemble or overlap with other disorders, including both Axis I and Axis II disorders?
3. What are the major commonalities in the etiology of the personality disorders? Which personality disorders have primarily developmental origin, and which have a strong potential genetic origin?
4. Identify specific cultural factors in your country/cultural environment that influence the understanding and treatment of certain personality disorder features.
5. What are the most striking gender differences among personality disorders – i.e., which disorders are, according to the text, most common among men, and among woman? How does that compare to your cultural experiences? Discuss reasons for observed differences
6. How does the prevalence of each personality disorder vary in your country/culture compare to those prevalence rates mentioned in the Module II text?
7. Discuss and compare the differences between treating personality disorders and Axis I disorders. How do co-occurring Axis I disorders influence treatment of a personality

disorder, and vice versa, how can the presence of a personality disorder affect the course and treatment of an Axis I disorder such as Bipolar disorder or Major Depression or Eating Disorder. Give examples.

8. Compare the major contemporary controversies of each personality disorder and discuss future changes in diagnostic classifications and important areas for research.

7.3.12 Recommended readings

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8 Eating Disorders

Eating disorders are serious mental illnesses that include potentially life-threatening behavioral, psychological, and physiological disturbances. Walsh and Fairburn define an eating disorder as "a persistent disturbance of eating behavior or behavior intended to control weight, which significantly impairs physical health or psychosocial functioning," and are not secondary to any recognized general medical or other psychiatric disorder (Walsh & Fairburn, 2002). While eating disorders are illnesses that primarily occur in parts of the world where food is plentiful, they have been reported on every continent, including in developing countries (Nobakht & Dezhkam, 2000; Pike & Mizushima, 2005). While more serious eating disorder cases, and those that present within geographic proximity to tertiary care medical centers, may be referred to specialists for management, most cases are initially identified, and frequently managed by pediatricians, internists, and other primary care clinicians. Eating disorders include anorexia nervosa (AN), bulimia nervosa (BN), and other conditions that in the current diagnostic system are categorized together as Eating Disorders Not Otherwise Specified (EDNOS). These EDNOS conditions include binge eating disorder (BED), night eating syndrome (NES), and sub-threshold syndromes in which some, but not all of the symptoms of the more formally defined eating disorders are present. This chapter will review the clinical manifestations, general epidemiology, and treatment options for the major eating disorders, including AN, BN, and BED.

9 Anorexia Nervosa

9.1 Clinical features and epidemiology

Anorexia nervosa (AN) is a serious psychiatric illness characterized by failure to maintain a minimally normal weight, intense fear of gaining weight or becoming fat, and preoccupations about body shape and weight. AN has a lifetime prevalence of approximately 0.5%-1% among women, and is estimated to affect one-tenth as many men (Hoek & van Hoeken, 2003). The onset of AN typically occurs in middle to late adolescence, the disorder being significantly more common in industrialized societies such as the United States and Europe than non-Western countries (Cummins, Simmons, & Zane, 2005; Eddy, Hennessey, & Thompson-Brenner, 2007; Hoek & van Hoeken, 2003; Pike & Mizushima, 2005). While the disorder has gained more public attention in recent decades, some version of AN can actually be traced back to the seventeenth century (Bell, 1987; Pearce, 2004). The defining psychological feature of AN is the relentless pursuit of thinness, which is often manifested by extreme weight control behaviors such as caloric restriction and excessive exercise. Associated with this severe dietary restraint, nearly 50% of individuals with AN also eventually develop episodic "loss of control" eating—that is, the aversive feeling that one is unable to stop or resist eating (Wilson, Grilo, & Vitousek, 2007). In AN, these loss of control episodes may be subjective, including small amounts more than what the individual intended to eat, or objective binges, including irrefutably large amounts of food consumed with discrete periods of time. Regardless of episode size, loss of control episodes may trigger purging behaviors, including self-induced vomiting and the abuse of laxatives or diuretics. However, these compensatory behaviors also may occur in the absence of loss of control eating. As a result of these extreme weight control behaviors, patients with AN maintain a body weight well below that which is minimally medically acceptable. Despite their low weight, patients often experience their bodies, or certain parts of their bodies, as too fat. This intense dissatisfaction with body shape and weight fuels a vicious cycle of weight loss and abnormal eating behavior that it is extremely difficult for individuals with AN to interrupt. The current edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-IV) has characterized AN using criteria that include the maintenance of low weight, the presence of cognitive distortions about body shape and weight, and the presence of amenorrhea for post-menarcheal females. There are two sub-types: restricting type, characterized by those who maintain low weight without any binge eating or purging behaviors, and binge-eating/purging type, characterized by the presence of binge eating or purging behaviors (see Table 1). While no specific weight threshold is identified for the AN diagnosis, DSM-IV includes an example of $< 85\%$ of recommended weight for height, and National Institute for Health and Clinical Excellence (NICE) guidelines suggest that body mass index (BMI) < 17.5 kg/m2 may indicate the presence of AN (American Psychiatric Association, 1994). In an attempt to improve diagnostic accuracy and inclusivity, draft criteria for AN proposed for DSM-5 include several changes (American Psychiatric Association, 1994). For example, the proposed

criteria for DSM-5 eliminate amenorrhea as a requirement for the AN diagnosis, as evidence suggests that menstruation, while a general indicator of nutritional status, does not provide meaningful clinical distinction among individuals with AN. Furthermore the amenorrhea criterion is not useful for important sub-groups of individuals with the disorder, such as women taking oral contraceptive pills, adolescent patients with primary amenorrhea, and men (Attia & Roberto, 2009). Individuals with AN, regardless of subtype, often suffer from numerous medical complications consistent with the hypometabolic and malnourished state, including bradycardia (sometimes with prolonged QTc interval), hypotension, hypothermia, and leukopenia (Attia, 2010). Common signs present in patients with AN include hair loss, the development of a downy hair growth on the face, neck and extremities (lanugo), salivary gland enlargement, indigestion, and constipation (Walsh, 2008). Electrolyte abnormalities, such as hypokalemia and hyponatremia, may also present, especially in individuals whose symptomatology includes vomiting or laxative abuse. Even in the presence of significant starvation, it is possible for individuals with AN to display normal laboratory values. Therefore, clinicians should not rely solely on laboratory results to assess acuity of illness. In addition to abnormal laboratory values, individuals with AN commonly display low levels of estrogen and testosterone. These hormonal changes often result in decreased libido, amenorrhea among females, and decreased bone density, eventually leading to potentially irreversible osteopenia and/or osteoporosis. Perhaps the most serious physiological change associated with AN is a prolonged QTc interval, which can lead to cardiac arrhythmia and/or sudden death.

Table 1. Diagnostic Criteria for Anorexia Nervosa, DSM-IV (American Psychiatric Association, 1994)

A) Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).B) Intense fear of gaining weight or becoming fat, even though underweight.C) Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.D) In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration).
Specify type:Restricting Type: during the current episode of AN, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).Binge-Eating/Purging Type: during the current episode of AN, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Psychological symptoms associated with AN include distractibility, agitation, and sleep disturbance, along with increased depression, anxiety, obsessionality, and compulsivity (Attia, 2010). In addition to these often transient symptoms thought to be associated with the state of nutritional compromise, many individuals with AN also suffer from comorbid psychiatric diagnoses. In a meta-analysis of the outcome of AN in the twentieth century, Steinhausen found that the majority of patients suffered from one or more additional mental illnesses at follow-up, most commonly anxiety and mood disorders, personality disorders, and

obsessive-compulsive tendencies (Steinhausen, 2002). However, it is important for clinicians to bear in mind that many symptoms of these comorbid disorders are exacerbated by the underweight condition, and thus may improve or even remit completely with the restoration and maintenance of normal body weight. In fact, studies of starvation in the absence of AN have been useful in identifying the myriad of ways that psychological symptoms develop and worsen in the context of malnutrition (Keys, Brozek, Henschel, Mickelsen, & Taylor, 1950). Historically, it has been very difficult to track the long-term outcome of AN for reasons including the lengthy course of the disorder and significant relapse rate among those who undergo acute weight restoration. The limited research that has examined longitudinal outcome of AN has revealed high relapse rates and only modest recovery rates. In a trichotomized system classifying outcome of illness into good, fair, and poor, 46.9% of patients reached full recovery from AN, 33.5% improved, and 20.8% displayed a chronic course of the disorder (Steinhausen, 2002). Patients with AN also displayed significant crossover to other eating disorders, most frequently BN and EDNOS (Walsh, 2008). Furthermore, the crude mortality rate amongst patients with AN has been estimated at 5.0% per decade of illness, a rate as high as that seen in any psychiatric illness (Sullivan, 1995). Among a large epidemiological sample of individuals with AN followed in Sweden, the overall mortality rate was 6.2%, with the most common causes of death for the sample being suicide, substance abuse, and eating disorder-related complications (Papadopoulos, Ekbom, Brandt, & Ekselius, 2009). While there are some limitations to the available data regarding longitudinal outcome in AN, there is strong empirically based consensus that AN is a serious mental illness associated with significant morbidity and mortality.

9.2 Etiology

Just as it has been difficult to track the long-term outcome of AN, the task of identifying the causal underpinnings of the disorder has proven to be equally challenging. The relatively low incidence and limited ethnic and gendered scope of the disorder, as well as the complicating medical and psychological consequences of semi-starvation, render AN a particularly difficult disorder to study in a controlled setting (Walsh & Devlin, 1998). Eating disorders have been proven to be more prevalent in women than men. For example Striegel-Moore et al. (2009) examined 3,714 women and 1,808 men and found that men were more likely to overeat than women. They found that around 1 in 5 women versus 1 in 10 men check their body size "very often". While the prevalence of eating disorders in cultures that idealize thinness suggest that social environment may play a causal role the development of the disorder, striking patterns of biological and psychological abnormalities in patients with AN suggest that multiple other factors also contribute (Attia & Walsh, 2009). Research has provided significant evidence for the role of genetic factors in the etiology of AN (Wade, Tiggemann, Bulik, Fairburn, Wray, & Martin, 2008; Bulik, Sullivan, Carter, McIntosh, & Joyce, 1999). Though specific genes have not been identified, the incidence of AN is greater in families with one affected member, and the disorder has higher rates of concordance in monozygotic than dizygotic twins. Heritable factors may also contribute to the development of AN more distally, through temperamental variables associated with the illness, such as perfectionism, obsessionality, compulsivity, and, particularly in the binge/purge subgroup, emotional lability (Walsh, 2008). In addition, numerous physiological disturbances, including abnormalities in the gastrointestinal tract and various hormonal and neurotransmitter systems, have

been considered as possible risk factors for AN (Walsh & Devlin, 1998). Researchers have speculated that leptin, a hormone that regulates appetite and metabolism, may play a role in the perpetuation of the illness, as leptin levels are typically low in underweight individuals with AN (Grinspoon, Gulick, Askari, Landt, Lee, Anderson, Ma, Vignati, Bowsher, & Herzog, 1996). Increased serotonergic activity has also been implicated in various behavioral and psychological characteristics of AN, including reduced food intake, perfectionism, and rigidity. Such evidence suggests that premorbid disturbances in this neurotransmitter might be a risk factor in the development of AN (Kaye, 2008). However, the influence of nutritional status on physiological processes requires caution in the interpretation of changes identified in AN, as these disturbances may be secondary to semi-starvation rather than contributing factors to the disorder's development (Walsh & Devlin, 1998). While specific causal factors have not been identified, investigators have made progress regarding some of the factors that may contribute to the perpetuation of the illness or the risk of relapse. Mayer et al. found that among inpatients who had fully restored their BMI to $>$ 20kg/m2, those with a higher percentage of body fat were less likely to relapse in the year following hospitalization (Mayer, Roberto, Glasofer, Etu, Gallagher, Wang, Heymsfield, Pierson, Attia, & Devlin, 2007). Furthermore, Schebendach et al. examined patients' food records obtained prior to hospital discharge and found that those whose diets had greater variety and higher energy density were more likely to have a good clinical outcome during the year following hospital discharge (Schebendach, Mayer, Devlin, Attia, Contento, Wolf, & Walsh, 2008).

9.3 Treatment of AN

Despite the fact that AN is an old illness, effective treatments continue to elude clinicians. Studies in this area are few, and none have identified clear empirical support for particular psychotherapeutic or pharmacologic treatments. In part, the challenges to treatment research in AN have resulted from features of the illness itself, including the low prevalence of AN in the general population, and the small percentage of individuals with AN who are treatment-seeking. These characteristics of AN make it difficult to recruit and retain adequate numbers of subjects for clinical studies (Wilson et al. 2007). Additionally, the medical issues present in AN make management difficult and expensive, further complicating efforts to rigorously study psychiatric interventions for this disorder. Treatment has evolved using various settings, including outpatient, day treatment, and hospital-based programs. It is generally accepted that treatment for AN needs to emphasize weight restoration. Behavioral management programs, aimed at normalizing weight and eating behavior, reinforce healthy behaviors and overall clinical progress with the use of consistently applied contingencies. While it is always desirable to utilize the least restrictive treatment setting in order to facilitate recovery, structured treatment programs such as inpatient, residential, and partial hospital programs may be necessary when outpatient efforts are unsuccessful or unavailable, or when medical or psychiatric status requires a higher level of care to assure safety. Inpatient treatment is often recommended for individuals who have rapidly lost a substantial amount of weight (usually defined by a weight below 75% ideal body weight for one's height, or a BMI of 16.5kg/m2). Voluntary treatment is also highly preferable, but involuntary arrangements may, at times, be appropriate, especially when a patient's weight falls into a medically dangerous range (Attia & Walsh, 2009). Treatment for AN should target full restoration of normal weight with associated resolution of physiological changes that may have developed in the context of

acute starvation. Healthy weight ranges are usually defined as being at least 90% of weight recommended for given height, but should consider pre-illness weight and weights at which normal physiological functioning such as normal menstrual activity is known to occur (Attia & Walsh, 2009). Treatment plans may include specific behavioral expectations (e.g., eat 100% of food that is prescribed by a treatment program, utilize staff observation and other treatment interventions aimed to help interrupt purging behaviors, achieve recommended weight gain, etc.). Failure to make clinical progress may be met with additional interventions aimed at increasing caloric intake and decreasing behaviors of illness. Examples of these interventions may include prescription of additional food or nutritional supplements, increase of supervision, and decrease of prescribed activity. Such interventions are not intended to be punishment for "bad behavior," but rather flexible changes to facilitate the ultimate goals of weight gain and recovery. In behavioral programs, patients are prescribed a diet of an adequate number of calories to achieve weight restoration. Approximately 3500 kcal over maintenance requirements are needed for every pound gained; therefore, sizeable numbers of calories are needed to achieve consistent weight gain. Treatment programs for AN differ in prescription of nutritional plan. Programs that achieve the typical weight gain rates of 2-4 lbs/week generally prescribe 3500-4000 kcal/day to patients at the peak of their weight gain needs. However, calories are typically started at a lower level and increased in a step-wise fashion in order to avoid refeeding syndrome, a syndrome consisting of serious, potentially life-threatening medical symptoms that may occur as refeeding begins and limited nutrient stores are tapped for catabolic processes (Attia & Walsh, 2009). Symptoms of refeeding syndrome may include hypophosphatemia, hypomagnesemia, significant fluid retention (both peripheral and visceral including risk of congestive heart failure (Mehanna, Moledina, & Travis, 2008). Risk factors for the development of refeeding syndrome include seriously low weight (e.g., BMI $<$ 16.5 kg/m2), recent precipitous weight loss, and metabolic disturbance upon presentation, including significant hypokalemia. It is recommended that physical status, including weight, presence of edema, and electrolyte levels be evaluated closely during the first two weeks of acute refeeding. The Columbia Center for Eating Disorders begins weight restoration treatment with a caloric prescription of 1800 kcal/day. Pending medical stability (generally determined within the first week of hospitalization), the daily diet is increased by 400 kcal every 2 to 3 days until it reaches 3800 kcal, 3000 kcal of which are provided in solid food and the remaining 800 kcal of which are provided in liquid supplement. Because a large part of treating AN emphasizes restoring not only weight, but normal eating behaviors, oral feedings are preferable to nasogastric ones whenever possible. However, this option may be considered for resistant patients, or those who do not enter treatment voluntarily. Patients in behavioral management programs are also offered a variety of therapeutic interventions from a multidisciplinary team of clinicians, commonly composed of physicians, psychologists, nurses, nutritionists, clinical social workers, and occupational therapists (Attia & Walsh, 2009). Treatment is aimed at confronting disordered eating behaviors and "feared" foods, as well as practicing normal eating. Meal and post-meal supervision, food shopping and cooking groups, and outings to local restaurants may be included in treatment programs to help patients process normal food selection and behaviors around eating with support from staff and peers. Additionally, patients generally participate in regular therapy and discharge planning sessions with psychologists, psychiatric residents, and social workers in individual, group, and family settings. Such structured and comprehensive behavioral programs are largely effective in helping patients with AN to normalize weight. Yet additional outpatient treatment dedicated to relapse prevention is generally necessary in order to maintain healthy eating and weight. Specific outpatient psychotherapies have been examined in AN, and

preliminary evidence supports one of these approaches—a family-based therapy (FBT) for adolescents with AN—as a potentially helpful intervention for outpatient weight restoration and maintenance. FBT, also called, the "Maudsley" method, named for an approach that was developed at London's Maudsley Hospital, assigns parents the responsibility of refeeding their child, utilizing many of the same treatment principles and reinforcements of structured behavioral programs. For adults, however, results with FBT have been less successful (Lock, 2001; Russell, Szmukler, Dare, & Eisler, 1987). Cognitive behavioral therapy (CBT) has also been studied in outpatients with AN, with more mixed results than that shown for FBT. CBT for AN was first described by Garner, Vitousek, and Pike in 1982 (Garner, Vitousek, & Pike, 1997). The regimen shares many basic therapeutic strategies with Fairburn's CBT model of BN (1985), but emphasizes the AN-specific issues of enhancing motivation, recognizing the problems associated with semi-starvation, and encouraging weight gain. In a small randomized controlled trial of 33 weight-restored women with AN, Pike et al. found CBT to be more helpful than nutritional counseling at preventing relapse (53% relapse among those receiving nutritional counseling versus 22% relapse among those receiving CBT) (Pike, Walsh, Vitousek, Wilson, & Bauer, 2003). However, a larger study using CBT together with fluoxetine vs. placebo for relapse prevention found that the entire sample had relapse rates of greater than 40% (Walsh et al. 2006). Additional studies have identified clinical improvement in those receiving CBT; however, it is unclear whether CBT fares any better than other specific psychotherapies for individuals with AN (McIntosh, Jordan, Carter, Luty, McKenzie, Bulik, Frampton, & Joyce, 2005; Ball & Mitchell, 2004; Channon, De Silva, Hemsley, & Perkins, 1989). Because individuals with AN commonly suffer from anxiety, depression, and obsessionality, medications that are generally helpful for these symptoms in other clinical populations have been studied in AN. Overall, results from these studies, most of which have examined antidepressant medications in small samples, have been disappointing (Attia & Schroeder, 2005). Preliminary evidence is more promising regarding the potential utility of olanzapine, an atypical antipsychotic medication, in the treatment of AN. Case reports, open treatment trials, and one small randomized controlled trial (Bissada, Tasca, Barber, & Bradwejn, 2008) suggest that olanzapine may help with both weight gain and alleviating psychological symptoms, namely obsessionality, for individuals with AN (McKnight & Park, 2010). The generally negative findings from studies of antidepressants in acute AN have led some to posit that the poor response to medication may result from the state of malnutrition and its influence on factors that affect medication response, such as neurotransmitter activity. As a result, medication studies in acutely weight-restored individuals have been conducted in order to examine the possible utility of medication at preventing relapse. Unfortunately, these studies have also failed to identify an effective pharmacologic treatment for AN. For example, a large, placebo-controlled medication trial conducted by Walsh et al. did not demonstrate any benefit from fluoxetine in the treatment of weight-restored patients with AN (Walsh et al. 2006). AN remains a challenging psychiatric condition for which a single clear, empirically-validated standard of care does not exist. There is no question, however, that weight restoration is an essential first step in treating this disorder, and that behavioral methods are often effective in facilitating this process. Medications alone are used less frequently in the management of AN, but are commonly incorporated as part of a multimodal approach to taking care of patients with this complex disorder.

10 Bulimia Nervosa

10.1 Clinical Features and Epidemiology

In contrast to AN, bulimia nervosa (BN) is a relatively new eating disorder, first described in the 1970s (Russell, 1979) and officially recognized by the American Psychiatric Association in 1980 (Walsh & Devlin, 1998). BN is defined by the frequent episodic consumption of objectively large amounts of food and the use of inappropriate compensatory behaviors to avoid weight gain. DSM-IV specifies that these episodes must occur at least twice weekly for three months in order to meet full diagnostic criteria for BN. A DSM-IV diagnosis of BN also requires overconcern with body shape and weight (American Psychiatric Association, 1994) (see Table 2). BN is more common than AN; an epidemiological review by Hoek and van Hoeken report a 1.0% aggregated prevalence rate for BN (Hoek & van Hoeken, 2003). Additionally, the gender ratio for BN reflects higher percentages of men affected than that seen in AN: 1.5% for females and 0.5% for males (Hudson, Hiripi, Pope Jr, & Kessler, 2007). Other studies have indicated even higher prevalence rates of 5-10% for more broadly defined manifestations of the disorder characterized by occasional binging and purging (Walsh, 2008). New diagnostic criteria being proposed for DSM-5 would lessen the frequency criteria of binge and purge episodes for BN to once weekly for three months, making it more likely that some of these sub-threshold cases currently classified as EDNOS would be considered full syndrome BN according to the proposed diagnostic system (American Psychiatric Association, 2010). Like AN, BN affects predominantly adolescents and young adults in industrialized societies (Fairburn & Harrison, 2003), however, the disorder has been described in a variety of non-Western cultures as well (Nobakht & Dezhkam, 2000; Pike & Mizushima, 2005). Though there is considerable overlap in the characteristics of AN and BN, these eating disorders are distinct from each other in several important respects. First, the characteristic feature of BN is that attempts to restrict food intake are interrupted by episodes of binge eating, during which individuals consume an unambiguously large amounts of food within discrete periods of time, and experience a sense of loss of control (Fairburn & Harrison, 2003). Binges are usually followed by purging, the most common methods being self-induced vomiting and the abuse of laxatives and diuretics. The frequency and intensity of these binge/purge episodes tend to escalate over time, enough so that many patients develop the ability to induce vomiting without mechanically triggering the gag reflex (Walsh, 2008). A small subset of patients with BN do not purge, but rather compensate for binge episodes with fasting and exercise. The combination of binge eating with extreme weight-control behavior generally places individuals with BN at a normal body weight, distinguishing them from those with AN, who are, by definition, underweight (Fairburn & Harrison, 2003). Because patients with BN typically present with a healthy body weight, the disorder has historically been associated with a significantly lower crude mortality rate (0.32%) than that described in AN (Steinhausen & Weber, 2009). However, results from a

recent study by Crow et al. have called this into question, describing mortality rates for BN as high as 3.9% (Crow et al. 2009).

Table 2. Diagnostic Criteria for Bulimia Nervosa, DSM-IV (American Psychiatric Association, 1994)

A) Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).B) Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.C) The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.D) Self-evaluation is unduly influenced by body shape and weight.E) The disturbance does not occur exclusively during episodes of Anorexia Nervosa.
Specify type:Purging Type: during the current episode of Bulimia Nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.Nonpurging type: during the current episode of Bulimia Nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

While there may be fewer medical risks of BN as compared with AN, BN also is associated with several potentially serious physiological complications. The most common medical problems in BN are dehydration and hypokalemia due to vomiting or the consistent overingestion of laxatives or diuretics. Hyponatremia and hypochloremia may be present, especially in individuals who replenish their fluid requirements with large amounts of plain water. Metabolic alkalosis may occur in individuals who purge by vomiting with the consequent loss of gastric acid. Conversely, acidosis may be present in those who abuse laxatives (Walsh, 2008). Individuals with BN may also develop a callus or scar on the dorsal side of the hand, commonly named "Russell's sign," due to the repeated impact of the teeth rubbing on the hand that may result from manual stimulation of the gag reflex (Halmi, 1987; Russell, 1979). In addition, the recurrent exposure to acid from vomitus may contribute to the gradual weakening of tooth enamel and eventual dental erosion causing a "moth-eaten" appearance of teeth. More serious consequences of bulimic symptoms such as esophageal tearing or gastric rupture have also been described (Walsh, 2008). As in AN, individuals with BN tend to present with psychiatric comorbidities (Steinhausen & Weber, 2009). In his meta-analysis of 79 studies of BN, Steinhausen identified mood and anxiety disorders, personality disorders, and impulsive behavioral disturbances, including substance use disorders and self-injurious behaviors, as pathologies frequently seen among patients with this disorder. In addition, Steinhausen found that patients with BN often cross over to develop other eating disorders (up to 32% of individuals studied). The most common crossover was to EDNOS, followed by AN, and finally BED, though it is suspected that crossover to this diagnosis is underreported, as BED was not yet officially recognized as a disorder at the beginning of the time period studied. Perhaps even more striking is the

fact that one-third of patients who present for treatment for BN have past histories of AN (Walsh & Devlin, 1998). The prognosis for individuals with BN is better than that seen in AN, although outcome studies suggest that significant numbers continue to struggle with symptoms of illness years after initial presentation (Steinhausen & Weber, 2009).

10.2 Etiology

Researchers have identified a range of biological, psychological, and environmental factors that might predict risk for the development of BN. First, there is good evidence that genetics may predispose certain individuals to BN. In fact, one study showed heritability to account for as much as 60% of variance in liability to the disorder (Bulik, Sullivan, & Kendler, 1998). Neurochemical abnormalities have also been described in BN, including those that, on a theoretical basis, offer support for several hypotheses regarding possible mechanisms responsible for the initiation and perpetuation of BN symptoms. Both the serotonergic system, involved in control of hunger and satiety, and dopaminergic system, central to the function of driven behaviors and reward, have been implicated in BN (Kaye, 2008). Additionally, research has shown the release of cholecystokinin, a gut hormone responsible for signaling post-meal satiety, to be blunted in BN (Devlin, Walsh, Guss, Kissileff, Liddle, & Petkova, 1997). A stomach relaxation reflex following the ingesting of a small liquid meal also appears to be lessened in BN, as compared with the normal gastric response seen in control subjects (Walsh, Zimmerli, Devlin, Guss, & Kissileff, 2003). Certain psychological characteristics have also been associated with BN. Specifically, depression, anxiety disorders, low self-esteem, and premorbid AN have been described in BN and have been examined as possible predisposing factors (Fairburn, Welch, Doll, Davies, & O'Connor, 1997). Discordant or weight-critical family environment, history of obesity, physical or sexual abuse, and the general cultural pressure to be thin are also thought to contribute to the risk for developing BN (Walsh & Devlin, 1998).

10.3 Treatment of BN

In contrast to the status of treatment research for AN, there is a solid evidence base for the treatment of BN. Many randomized controlled trials have been conducted successfully in BN, identifying both pharmacological and psychological interventions that are effective at reducing or eliminating the core symptoms of BN. Systematic reviews of available treatment studies consistently conclude that cognitive behavioral therapy (CBT) as well as antidepressant medications are both effective for short-term management of BN (Shapiro, Berkman, Brownley, Sedway, Lohr, & Bulik, 2007).

10.4 Psychological treatments for BN

CBT—specifically, a form of CBT that focuses on identifying, examining, and modifying a cycle of interrelated thoughts and behaviors that maintain the eating disorder—has been found consistently to be helpful for BN (Fairburn, 1985). For example, patients with BN may describe cognitions that support a connection between self-evaluation and

body shape and weight. These thoughts and beliefs may lead individuals with BN to excessive dietary restriction and inappropriate weight control behaviors in order to affect self-evaluation. This process of restricting, in turn, predisposes individuals to binge eating and purging, which has the ultimate consequence of worsening self view and reinforcing the eating disordered behaviors. CBT sessions for BN focus on identifying inconsistencies in the patient's established cognitions and related behaviors in order to help identify alternative thoughts and healthier behaviors. This treatment typically involves 20 sessions that take place over the course of 4-5 months, and has been utilized in both individual and group settings. CBT appears to be associated with lasting cessation of binge eating and purging in 30-50% of BN cases, with many others achieving substantial improvements not only in binge/purge symptoms, but also in self-esteem, social functioning, and general psychological well-being (Wilson et al. 2007). Another outpatient psychotherapy shown to be helpful in BN is interpersonal therapy (IPT), a short-term, structured treatment originally developed for depression (Klerman, Weissman, Rounsaville, & Chevron, 1984) and adapted by Fairburn for BN (Fairburn, 1993). This intervention does not focus directly on eating disorder symptoms, but rather emphasizes current interpersonal problems that are thought to be maintaining the eating disorder. Though CBT, based on the empirical and clinical evidence, is generally the preferred treatment for BN, the NICE (2004) guidelines have recommended that IPT be considered as an alternative to CBT (Wilson et al. 2007). While evidence-based psychotherapies, like CBT and IPT, are consistently effective in clinical trials, these specialized treatments have not been successfully disseminated to community practitioners. A shortage of therapists trained to deliver these treatments impedes access to evidence based interventions for many individuals with BN. There has therefore been interest in whether self-help versions of CBT may be more accessible and cost effective options for BN treatment (Wilson et al. 2007). In fact, there is some evidence that Guided Self Help (GSH) options that provide support and information to the user of a self-help manual may be useful for a subset of individuals with BN, and may be an alternative for those who do not have access to specialist treatment options (Grilo, 2000).

10.5 Pharmacotherapy for BN

Several medications are helpful in the treatment of BN. The high rates of comorbidity with depression seen in BN led to initial attempts to treat this eating disorder with antidepressant medications. Randomized controlled trials using antidepressant medications, initially examining monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), began soon after the first published descriptions of BN. These trials consistently found benefit associated with antidepressant compared with placebo at reducing binge eating and purging behaviors in BN samples (Broft, Berner, & Walsh, 2009). The more favorable side effect profile of the selective serotonin reuptake inhibitors (SSRIs) led to more trials using these medications once they became available. In fact, following a large multi-site trial that demonstrated medication efficacy in 387 individuals with BN, fluoxetine became the only medication approved for use in BN by the U.S. Food and Drug Administration (Walsh, 2008). It is of note that the dose of fluoxetine recommended for BN (60 mg) is higher than that typically used in treating depression, and also that antidepressant medications are effective at treating BN irrespective of depression symptoms (Walsh, Gladis, Roose, Stewart, Stetner, & Glassman, 1988). Other classes of medication have also been studied for

possible utility in treating BN. Specifically, topiramate, a medicine used to treat seizures that has been found to suppress appetite and cause weight loss, has been examined in BN and associated with benefit in several studies (Hedges, Reimherr, Hoopes, Rosenthal, Kamin, Karim, & Capece, 2003; Hoopes, Reimherr, Hedges, Rosenthal, Kamin, Karim, Capece, & Karvois, 2003; Nickel, Tritt, Muehlbacher, Gil, Mitterlehner, Kaplan, Lahmann, Leiberich, Krawczyk, & Kettler, 2005). However, cognitive side effects and paresthesias associated with topiramate lessen its acceptability to BN patients compared with SSRIs. Odansetron, a medication used primarily for the treatment of nausea in medical and surgical settings, has been tried in one small trial of BN with some benefit (Faris, Kim, Meller, Goodale, Oakman, Hofbauer, Marshall, Daughters, Banerjee-Stevens, & Eckert, 2000). Although medications (most commonly SSRIs) are useful for short-term management of BN—especially those who have not responded to CBT as a sole intervention—there are few data to support continued efficacy over the long-term (Nakash-Eisikovits, Dierberger, & Westen, 2002). Several studies do support the enhanced effect of combining medication with CBT for treatment of BN, and some authors suggest that multi-modal treatment is the approach most likely to be associated with long-term remission and symptom reduction rates (Wilson et al. 2007). For patients with BN who do not respond to evidence based outpatient approaches, many of whom present with psychological co-morbidities or multi-impulsive behaviors, more intensive forms of treatment, such as hospital-based and day treatment may be necessary (Walsh, 2008). Inpatient hospitalization programs for BN typically aim to break the cycle of binge eating and purging, and are followed whenever possible by additional treatments that support the continuation of structured eating, strategies to prevent or reduce likelihood of post-meal purging, and weight maintenance. As with AN, inpatient programs for BN generally include several treatment approaches offered by a multi-disciplinary team of clinicians.

11 Binge Eating Disorder

11.1 Clinical Features and Epidemiology

Binge eating disorder (BED) is characterized by repeated, persistent episodes of binge eating in the absence of the inappropriate compensatory behaviors seen in BN. According to DSM-IV diagnostic criteria, BED is defined by the consumption of unusually large quantities of food in discrete periods of time together with the experience of loss of control over eating. DSM-IV also specifies that binge eating in BED is associated with emotional distress, and must occur at least twice a week for six months to meet full diagnostic criteria (American Psychiatric Association, 1994). Currently a provisional diagnosis under the larger heading of EDNOS in the DSM-IV, BED is being proposed as a distinct eating disorder in the upcoming DSM-5 (American Psychiatric Association, 2010). In contrast to both AN and BN, BED is seen most frequently in middle-aged individuals, and is evenly distributed across gender and racial demographics, though there is some evidence to suggest that women may be more likely to present for treatment (Tanofsky, Wilfley, Spurrell, Welch, & Brownell, 1997; Wilson et al. 2007). BED is also distinct from the other eating disorders in that binge eating occurs in the context of general overeating as opposed to a setting of dietary restraint (Fairburn & Harrison, 2003). Because of the nature of its symptoms, BED has a strong association with obesity. Although present in approximately 3% of adults, the disorder has a higher prevalence among obese individuals (Grilo, 2002). In fact, BED is present in as many as 5-10% of patients seeking weight control treatment (Fairburn & Harrison, 2003). Because of its links to obesity, BED is associated with increased mortality and risk for numerous medical disorders, including hypertension, diabetes, respiratory illness, cardiac problems, and osteoarthritis (Wonderlich, Gordon, Mitchell, Crosby, & Engel, 2009). It is important to remember that individuals with obesity do not necessarily suffer from BED. Research has identified a distinct set of psychological characteristics that distinguish patients with BED from obese individuals who are not affected by the disorder. Compared to obese individuals without BED, those with BED report increased rates of depression, anxiety, and dissatisfaction with shape and weight similar to that seen in BN (Walsh, 2008; Yanovski, 1993). Individuals with BED also report a lower health-related quality of life, less life satisfaction, and more functional impairment than obese individuals without eating disorders (Wonderlich et al. 2009). Moreover, eating behavior studies have found that, when instructed to binge eat in a laboratory setting, individuals with BED eat more than their obese counterparts without the disorder (Yanovski, Leet, Yanovski, Flood, Gold, Kissileff, & Walsh, 1992; Goldfein, Walsh, Devlin, Lachaussée, & Kissileff, 1993; Sysko, Devlin, Walsh, Zimmerli, & Kissileff, 2007). Such evidence confirms the meaningful diagnostic and clinical distinction between binge eaters and non-binge eaters within the obese population. In preparation for the upcoming publication of DSM-5, there has been extensive debate about whether the current data available about BED support its identification as an eating disorder separate from the EDNOS category. In their review of BED, Wonderlich et al. argue that

the consistent clustering of disturbed eating symptoms in affected individuals, together with the psychological distress, functional impairment, and significant rates of psychiatric comorbidity associated with BED, support its meeting the definition of illness (Wonderlich et al. 2009). In contrast to AN and BN, BED appears to have a shorter and more variable course. BED is associated with both high rates of treatment response and the possibility of spontaneous resolution of symptoms, but also possible symptom recurrence. Patients with BED are less likely to cross over to another active eating disorder than are individuals with AN or BN. Together, this evidence paints a portrait of BED as a variable, yet sometimes chronic disorder that often fluctuates over time.

11.2 Etiology

While researchers speculate that biological, psychological, and environmental factors contribute to the development of BED, as they do other eating disorders, the specifics of these risk factors for BED are still relatively poorly understood. Research does indicate that presence of obesity increases an individual's likelihood of developing BED (Fairburn, Doll, Welch, Hay, Davies, & O'Connor, 1998). Additionally, there is preliminary data to suggest that BED runs in families, with heritability ranging between 0.39 and 0.57 (Hudson, Lalonde, Berry, Pindyck, Bulik, Crow, McElroy, Laird, Tsuang, & Walsh, 2006; Javaras, Laird, Reichborn-Kjennerud, Bulik, Pope, & Hudson, 2008). These substantial familial associations implicate a potential additive effect of genes on the development of BED. However, research has yielded mixed evidence regarding the preexistence of chemical or neurological abnormalities in individuals with this disorder. Though some early studies have yet to find any distinct neurochemical or hormonal anomalies among binge eaters, others tentatively associate BED with decreased levels of the hunger-stimulating hormone, ghrelin (Geliebter, Gluck, & Hashim, 2005). An individual's development of BED may also be influenced by numerous non-specific risk factors for psychiatric disorders, such as parental depression and adverse childhood experiences (Fairburn et al. 1998).

11.3 Treatment of BED

Treatment of BED usually aims to help patients normalize eating behavior, with any weight loss achieved being secondary to the behavioral improvement. While excess weight clearly represents a significant medical problem for some individuals with BED, it is uncertain whether these individuals receive the same level of benefit (i.e., lasting weight loss) from behavioral weight loss treatment programs as non-binge eaters. Hence treatments that aim to improve binge eating behavior are typically recommended when BED is also present in the overweight or obese state (Wilson et al. 2007). Specialized psychotherapies have been shown to be helpful in addressing the psychological symptoms of BED. Both CBT and IPT are reliably effective in eliminating binge eating and reducing eating disorder psychopathology both in the short and long term. Although these specialized psychotherapies do not typically yield clinically significant weight loss, they do often prevent further weight gain by reducing or eliminating binge eating behavior (Wilson, Wilfley, Agras, & Bryson, 2010). Specifically, there is strong empirical support for the use of a form of CBT in BED. Adapted from Fairburn's CBT for BN, this specialized treatment emphasizes recognizing and modifying

unhealthy eating patterns (Fairburn, Marcus, & Wilson, 1993). CBT for BED is associated with a high treatment completion rate (approximately 80%), as well as remission from binge eating in 50% of patients, and general improvements in depression and other psychosocial impairments. IPT has been shown to be about equally as effective as CBT for treating BED in both the short and long term (Wilson et al. 2007). Finally, dialectical behavior therapy (DBT) is a specialized treatment that focuses on emotional regulation and gaining greater awareness of chaotic eating habits that characterize BED. While it does not boast as strong of empirical support as CBT and IPT, DBT seems to be a well-suited and durable alternative treatment for BED (Telch, Agras, & Linehan, 2001). However, the high cost of these specialized treatments, along with the limited availability of therapists who are adequately trained to perform them, has prompted researchers to investigate more accessible, cost-effective treatment options for BED. Wilson et al. found a mode of guided self help based on CBT (CBTgsh) to be equally as effective as IPT in eliminating binge eating in both the short and long term (Wilson et al. 2010). It is of note, however, that, neither CBTgsh nor IPT produced as much weight loss as did a separate behavioral weight loss treatment. In addition to psychotherapies, researchers have examined the efficacy of various medications in the treatment of BED (Bodell & Devlin, 2009). Consistent with evidence from combined treatment studies of BN, Devlin et al. found CBT to be more effective than fluoxetine as adjunct treatments to group behavioral weight loss treatment. While the addition of fluoxetine to CBT provided little if any improvement in binge reduction, the medication did decrease psychopathologies often associated with BED, such as anxiety, depression, and dietary restriction (Devlin, Goldfein, Petkova, Jiang, Raizman, Wolk, Mayer, Carino, Bellace, Kamenetz, Dobrow, & Walsh, 2005). Leombruni et al., on the other hand, found sertraline to effect a significant improvement in both binge behavior and binge frequency, as well as clinically significant weight loss for up to 24 weeks in women with BED (Leombruni, Piero, Brustolin, Mondelli, Levi, Campisi, Marozio, Abbate-Daga, & Fassino, 2006). Still other evidence from pharmacotherapy studies of BED suggests high and rapid rates of relapse, as well as simple noncompliance with extended open-label treatments (Wilson et al. 2007). The numerous characteristics of BED that distinguish it from AN and BN render it a subject of unique interest within the field. Because formal research on BED is in relatively preliminary stages, there is still much to learn about its etiology, symptomotology, and treatment. Future efforts would be well-directed towards studying the longitudinal course of the disorder, untangling the complex issues of its management, and further exploring biological and psychological factors that put individuals at risk for developing BED.

12 Conclusion

Eating disorders, including AN, BN, and BED are serious conditions in which significant disturbances in eating behavior are accompanied by distressing cognitions about body shape and weight. They are all illnesses with physical, as well as psychological manifestations. Once their symptoms are established, eating disorders may contribute to significant functional impairment, and are often very difficult to interrupt. Evidence-based treatments, including pharmacotherapy and CBT, are helpful in the treatment of BN and BED, but additional research is needed to establish empirically-supported treatments for AN, the eating disorder with the highest rates of morbidity and mortality.

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14 Disorders of Childhood & Adolescence

14.1 Introduction

Children cannot be considered to be little adults. Child and adolescent psychiatry is a unique area and conceptualisations typical of adult mental health are often either not helpful such as the rubric of personality disorders, or fall short in terms of emphasis. For example whilst adult practitioners will consider the patient's family, in childhood and adolescence the family may be a source of solutions that lead to symptom reduction, a barrier to change or indeed the cause of the child's presentation.

Child and adolescent psychiatrists conceptualise their patients and their patient's challenges in a unique way. This focuses on the twin concepts of development, the changes that occur as part of growing up, and of the inter-relatedness of the child and those around them which as a shorthand can be called the systemic perspective.

To elaborate, a fundamental task of infants, children and adolescents is to grow and in so doing learn to regulate, or achieve mastery over physiological, behavioural and emotional systems such as the ability to sleep, eat, self-soothe and control the excesses of behaviour and impulsivity. As adults we do not, and cannot live life as "toddlers" and few adults would tolerate temper tantrums in their work colleagues. A developmental perspective allows the child and adolescent psychiatrist to know that stranger danger in a baby is normal and separation anxiety for the first few days of school is also within the normal limits. Similarly, the child and adolescent psychiatrist knows there should be a gradual improvement in the young boy's ability to sit still and attend in class. Not to do so may suggest pathology. A grounding in what abilities and limitations to expect of children and adolescents, by age, gender and influenced by cultural expectation is essential to working in this area.

The content of some child and adolescent conditions demonstrate a developmental presentation pattern. For example, an underlying vulnerability to anxiety may become manifest in different ways across the child and adolescent developmental span. Of the anxiety-related presentations early issues include prolonged and excessive stranger danger; in the older child prolonged school-related separation anxiety. In pre-school children phobias often manifest as a fear of animals, in early school-age children as fear of the dark and/or burglars, school phobia around the age of entry to high school, in adolescence social phobia and late adolescence sees the onset of agoraphobia and panic disorder.

A systemic perspective emphasises that infants, children and adolescents are not "islands," indeed the very young cannot live without the care and protection of adults. Further, children develop within systems or social networks, most obviously the immediate and extended family and the school environment, the latter including peers and teachers. Included in such understandings will be culturally dependent rules such as how extended is the typical family. For example, is it the norm for grandparents to live with the child and parents; how open or

closed is the family to non-familial influences such as the impact of religious or village leaders and the influence of the media. As well as the generally applicable culture within which the family sits there are patterns of interaction and belief which may be more individual to the particular family and not necessarily shared by their neighbours. The parents may be in conflict and the child caught in the middle. A parent may be chronically ill and the child adopting a carer role. Understanding of both individual family systemic issues and the wider cultural influences are important to the practice of child and adolescent psychiatry in a variety of ways. In terms of engagement for instance one must to know whether it is appropriate to conduct a home visit, how to address parents and grandparents and what sort of formulations are likely to make sense to the child and family. A systemic perspective is also important to management. This is universal in child and adolescent psychiatry, not restricted to cases where the treatment modality is family therapy. Clearly an intervention that contravenes a local or family belief is unlikely to be supported by the family, and is therefore unlikely to be successful.

Biological thinking, whilst in children less likely to lead to pharmacological interventions, is highly relevant to child and adolescent psychiatry. Biological constructs that may be important to a child's mental health presentation include a history of any pathological processes that may have affected the child's developing brain. Examples include infections and toxic insults during pregnancy or anoxic brain damage during labour or the first minutes of life. The child and adolescent psychiatrist routinely takes a history about such issues, as well as considering the child's facial and body morphology for possible chromosomal or genetic abnormalities, and any evidence of developmental delay during the early years. Developmental delays may be circumscribed but more commonly may cross functional domains so a broad and comprehensive assessment is required. It will be found, for example, that many children with behavioural problems are also clumsy. Developmental problems, even though due to problems before or around birth, may not manifest themselves immediately. For example a lowered intelligence or specific learning or speech problems may not become obvious until the child enters the late preschool or early school period. In adolescence biological issues that arise are less likely to be developmental and more likely to be the adverse mental health effects of injury or misadventure, or related to the development of an acute or chronic medical illness such as diabetes or drug use and abuse.

Later in this chapter issues of disease classification relevant to child and adolescent psychiatry will be discussed. The preceding introductory comments may lead some readers away from classifications that are primarily categorical such as the ICD-10 and DSM systems. These classifications are important in child and adolescent psychiatry and facilitate good communication, research and service planning. However, child and adolescent psychiatrists are equally influenced by and comfortable with dimensional views of psychopathology. For example, where the child lies on a dimension of inattention is as important as is the question as to whether the child has Attention Deficit Hyperactivity Disorder. A dimensional view has the added benefit of potentially being less "pathologising" in that embedded in this approach is the understanding that healthy children also have a degree of "whatever it is" (i.e., inattention) but either have a more "healthy" amount or are more able to cope with it. With this perspective, rather than seeking cure of a categorical disorder, the child and adolescent psychiatrist will work to help the child and family move towards a more functional developmental trajectory. An example of this might be, in the case of a child with attention deficit, to attend more to the need to achieve education and less to the treatment

of symptoms. This might, for instance, lead to the planning of a medication regime in a way which gives maximal attentional enhancement when the child is in school.

A useful dimensional nosology often used in child and adolescent mental health is the distinction between internalizing and externalizing symptoms. Formally derived from the scoring system of the Child Behavior Checklist (CBCL: Achenbach, 1991) and related measures, this terminology has now entered more general usage. Externalising symptoms are clearly witnessed or reported, obvious to an observer whereby the child will "externalise" an assumed feeling state, cognition or demonstrate lack of age-appropriate regulation. Typical symptoms include anger, aggression and hyperactivity. Internalising symptoms are less obvious, indeed may go unreported without appropriate questioning. Typical internalizing symptoms are depressed mood and specific and generalized fears.

14.2 Phenomenology

14.2.1 Epidemiology

Population based surveys across numerous countries and cultural groups have recorded the prevalence of mental health disturbance in children and adolescents at between 15 - 20%. Methodological and design issues include whether the research was primarily parent report which finds higher rates of externalising disorders; child and youth self-report which provides better estimates of internalising disorders; or more robust designs which included information from multiple informants. General trends include higher rates of externalising disorders in males and of internalising disorders in females. Often, as is the case with depression, gender-based rates are similar in the pre-pubertal period. Post-puberty rates of depression are higher in females. Some conditions present at specific developmental stages, for example early onset psychosis is rare before the middle teenage years, or demonstrate a clear developmental relationship or progression. An example of the latter is the common trajectory from oppositional defiant disorder (ODD) in children to conduct disorder in adolescents.

It is probable there are many reasons for cross-cultural differences in the prevalence of specific conditions. One is that the prevalence of illness/disorder will be influenced by local conditions; anorexia nervosa is more common in affluent developed world. Another is the willingness to diagnose depends on culture; what was naughtiness in some western societies is now ODD or ADHD. With these caveats in mind useful prevalence estimates include a rate and diagnosable depressive disorder of approximately 3%, anorexia nervosa 0.5%, ADHD 6%, ODD and CD 6-10% (increasing with age) and autism 0.1%. Note one cannot simply add these prevalence figures and conclude that most children have a mental health problem. Conditions are often comorbid with one individual sometimes experiencing two or three mental health disorders.

Another consideration is impairment. Many symptoms such as mild anxiety, brief lowered mood or nightmares after a traumatic event are often normal. Key to the diagnosis and subsequent management plan is the impairment in daily functioning. If symptoms interrupt the child's family or peer relationships, or impede their ability to attend and take advantage of school and other activities i.e., if symptoms either prevent normal function or normal development, then the presentation is more serious and worthy of an intervention. One

measure of impairment is the disability adjusted life years (DALY) methodology. A recent application of this methodology to the child and adolescent mental health area suggests the impairment burden of neuropsychiatric conditions in children will double by the year 2020.

14.2.2 Clinical symptoms and classification

A major issue differentiating child and adolescent psychiatry from practice with adults is that the content of symptoms varies across the child and adolescent developmental span. Consider the example of depression. The symptoms displayed by older adolescents are often identical to the adult criteria for a major depressive disorder, for example a pervasively lowered mood, often with diurnal mood change, anhedonia, neurovegetative changes in sleep, appetite, weight and energy and typical depressive cognitions of helplessness, hopelessness and possibly suicidal thinking. This is very different from the picture seen in younger children. An eight year old, for example, can become profoundly depressed in mood without much in the way of depressive cognitions and is unlikely to report suicidal thinking. The very young child may seem sad without much verbal elaboration, relatively mute and markedly withdrawn with no pleasure in play or during other typical childhood activities. Uncertainties over whether a low mood in a younger child without significant depressive cognitions is the equivalent of a more adult type picture in an older adolescent, have, in the past, and perhaps in the present too, lead to difficulties in making valid diagnoses particularly in the younger age group.

Another group of disorders which show considerable variation with age are the anxiety disorders. Fear of the dark is so common in very young children as to be normal. However, with increasing age fears become more related to social interaction such as fear about being asked questions or giving presentations in class, difficulties talking to peers, or to adults when attempting to buy food, clothes or bus tickets. Similarly, age differences are seen in the anti-social domain; younger children rarely engage in assault with weapons or force others into sexual activity, these are features of conduct disturbance in older age groups.

Often clinicians will ask screening questions about typical externalising and internalising symptoms. Considering the former, disruptive young children are oppositional, defiant, easily angered, have prolonged or severe tantrums and actively defy authority figures. Older children and adolescents engage in aggressive behaviour: fighting, bullying, sometimes using a weapon, cruelty to animals or forcing others into sexual activity. They may also steal or vandalise property. The oppositional defiant behaviour seen at a younger age may also persist into adolescence. Other common behavioural presentations are inattentive and/or hyperactive behaviour which may occur in isolation or co-occur with aggressive or defiant behaviour. Children with these symptoms may demonstrate problems with their ability to maintain age-appropriate attention and concentration, problems controlling impulsivity or demonstrate hyperactive behaviour. "Age-appropriate" is a key construct in that there may be a considerable gap between this and the behaviour expected by parents. The latter can be either too permissive or inappropriately demanding for the child's developmental stage. The symptoms are often prominent in classroom settings; they are of greater significance if they are present across numerous settings, typically including home and school. Hyperactive symptoms include the sense that child is always moving, cannot remain still even for an enjoyable activity and the behaviour may lead to dangerous play with risk of injury. Another group of behavioural presentations are the stereotypical, repetitive behaviors such as hand twirling or flapping or unusual mannerisms seen in children with autism and pervasive

developmental disorders. Such behaviours have no functional significance, begin early in life and often persist. These behaviours should be differentiated from tics, for instance seen with Tourettes disorder or from medication side effects such as may be caused by some anti-psychotic medication. Autistic children may also demonstrate hyperactive and aggressive behaviours.

Internalising symptoms are often considered to be synonymous with anxiety and depressive symptoms. However, a broader definition is probably more useful. This would for example, include the body image disturbance typical of eating disorders. Many internalizing symptoms have been previously mentioned in this chapter. Childhood fears are common. In young children these are often poorly elaborated fearful feelings. With increased age they may be associated with cognitions typical of panic such as pre-event wishes to avoid the situation, or feelings that symptoms such as tachycardia are evidence of impending physical illness or death. Other common anxiety symptoms of children are obsessional thoughts, especially about germ's or poisons, fears about school, and nightmares seen in Post traumatic stress disorder (PTSD). As with anxiety, depressive symptoms too change with age. In younger children they are not specific, and often take the form of a desire to withdraw and be alone and a general lowered mood. With age the child may become more pessimistic, hopeless and feel they are worthless or incompetent. From the mid-teen years onwards suicidal thoughts are common. These are of more concern if the thoughts are accompanied by detailed planning and a desire to enact the plan. In children and adolescents it is useful to identify the symptom of anhedonia (loss of the typical pleasure response). It is unusual for primary-school age children to avoid parties or activities and lose interest in interacting with friends. Adolescents can often describe an altered sense of pleasure; the younger child may not be able to describe this change. However, parents are often able to report this phenomenon as altered behavior – parents notice the child does not take as much pleasure in their usually enjoyed activities.

It is beyond the scope of this chapter to discuss all symptoms seen in child adolescent psychiatric practice. Many low prevalence conditions have typical or pathognomic symptoms such as eating non nutritious substances (Pica), being persistently mute despite normal speech and vocalisation apparatus, especially when outside the home environment (Selective Mutism), deficiencies in reciprocal social awareness and behaviours (Autism and Pervasive developmental disorder), tics, encopresis, enuresis and disturbances of attachment to name some. A comprehensive child adolescent mental health text is recommended to further study such conditions.

Attachment related symptoms are common and require some comment. Infants, including very young children are innately social and from birth demonstrate a repertoire of behaviours that promote attachment to parents, primary caregivers and other adults. Normal, adaptive, "secure" attachment behaviour is demonstrated by the infant maintaining suitable proximity to the parent, a willingness to explore the environment whilst repeatedly seeking assurance and a developing ability to self-soothe during brief periods of separation. Attachment styles where the infant is more anxious, ambivalent or disorganized include infants who are overly vigilant and excessively watchful, overly withdrawn or inconsistent in developmentally appropriate social interactions. Such behaviours are more likely to cause both current difficulties with establishing eating and sleeping and other routines, as well as the infant being more likely to develop mental health problems during later childhood.

14.2.3 Assessment

As previously mentioned, as a generalisation children live within a family context and so it is usual to begin with interviewing the whole family. If there are no biological parents then the child is seen with the usual caregivers; for orphaned children the child is seen with the adult responsible for their care. Again, the practitioner needs to be knowledgeable on the child's developmental stage and what are the usual capacities and competencies for a child of that age. Importantly, this includes knowledge of the communication style and ability that would be expected. Some practitioners are fortunate in that they have been personally exposed to caring for young children in non-clinical settings. If this is not the case the practitioner can be guided by the type of school activities that are typical for children of different ages and school grades. For example, very young children in the school setting are often engaged in creative activities. Play is the primary communication mode of young children. Older children will draw, colour in or engage in imaginary play with toy figures. Towards the end of primary school children will more readily engage in conversation, although will often give few details spontaneously. Guiding the conversation with drawings or timelines or an activities leads to greater richness of detail. Adolescents will usually engage in greater self reflection and prolonged conversation and are often seen before other family members to emphasise their progress towards individuation from the family. Cultural issues are important when considering what information should come from father or mother and whether children should be seen by themselves or only when other family members present.

14.2.4 Pathogenesis

An approach seen across many areas of psychiatry is the biopsychosocial-cultural schema. This schema emphasises the child lives within a family, school, local environment context and there may need to be interventions at numerous parts of the individual and social ecology to achieve a successful outcome. Rather than consider biopsychosocial-cultural factors during the infant, child, early and late adolescent stages separately, this section will take an over-arching developmental view and integrate these various ecological influences at different stages of development.

A developmental approach acknowledges differences in the child's integration of biological, emotional, cognitive and behavioural systems and differences peer and family interactions across the life span. Developmental theory highlights it is the interplay of these factors that determines whether development approximates to the normal trajectory or whether deviation occurs. The later, if significant, is synonymous with the presence of symptoms and impairment. The "normal trajectory" does not imply there is a single pathway to a particular outcome. Critical aspects of the biopsychosocial frame are required, including for example an intact central nervous system, availability of at least one attachment figure and an environment with the potential of providing at least food and shelter. Other useful concepts in the developmental context are protective, resilience or vulnerability factors. We will refer to descriptors for the major development epochs: fetal, infant, child and adolescent periods, despite some conjecture about when difference stages begin and end. Developmental is, after all, continuous.

Biological fetal determinants of later mental health include toxic fetal environmental factors and the adverse effects of maternal malnutrition. Toxic effects can be from infections (e.g., rubella, herpes, human immunodeficiency virus, cytomegalovirus and toxoplasmosis); excessive maternal alcohol intake and deficiency states such as folate deficiency, the later commonly following malnutrition. Genes controlling major organogenesis are operant during the fetal period and toxic effects at this stage can be catastrophic including mal-development of the central nervous system. Although birth-weight may give some indication of the success and traumas of the gestational period it is a very coarse and non-specific marker. However, intrauterine growth retardation (measures of which include both birth-weight and gestational age) is a useful predictor of later hyperactivity, academic performance and possibly other outcomes. Important psychosocial factors during the fetal period include maternal perception of social support, the development of attachment to the developing fetus and whether the wider system such as father, grandparents and wider community are involved or supportive.

The infant phase is obviously influenced by persisting fetal factors. From a mental health perspective a psychological construct of major importance in this stage is attachment. Attachment theory has essentially either replaced or lead to profound modification of previously held psychodynamic and learning paradigms. Understanding of attachment has progressed with recent cognitive and developmental psychology research finding the infant's competence is greater at an earlier age than previously thought. Early behaviours include the infant's ability to recognise their mother's voice in the hours after birth and preferential eye tracking around two months of age. One must remember attachment is not uni-directional but rather relates to the relationship between infant and primary caregiver. Attachment has both cross-sectional and longitudinal links with mental health. Up to 80% of the offspring of depressed mothers display insecure attachment. This attachment style is also related to the child's delayed expressed language and cognitive development.

As is expected the childhood period continues the development of the infant period including the attachment pattern established at that time. The child period is a time of continued cognitive, speech, language and psychological development underpinned by continued synapse formation, continuous (CNS) reorganisation and maturation of neuronal circuits. It is a time of an increased sense of self-efficacy, competence and mastery of more complex social circumstances. Social development includes a move from solitary play to parallel and then cooperative play, with the locus of contact not solely restricted to the family home. Relationships with non-family individuals such as school friends become more common, complex and incorporate increasing imagination and fantasy. Peers and group membership become important and the experience of rejection by peers can have major consequences including development of anxiety and lowered mood. Indeed children can develop both depressive and anxiety disorders of a degree of severity which justifies professional intervention. Consequences can include impaired social relationships, diminished social support, diminished self-esteem and increased deviant behaviour. These can then in turn result in further deterioration of the child's mental state with a resulting downward spiral. Conversely, childhood can be a time of an increased sense of self-efficacy, competence and mastery of more complex social circumstances such as interactions in the school domain.

Definitions of Adolescence vary are often culture bound. One could argue that adolescence, or at least its recognition as a significant developmental stage is a relatively recent phenomenon and one of most relevance to the affluent developed world. There are many societies where

work, marriage and the taking on of adult type responsibilities, unfortunately including going to war, occur at ages where the typical western teenager is engrossed in adolescent experimentation and is very far from these things.

From a biological perspective the onset of adolescence is defined by the hormonal changes of puberty and the effects these changes have on body morphology including the development of secondary sexual characteristics. Behaviour is in part gender-specific with greater levels of aggression in males and depression in females. Biological influences during the adolescent stage are not limited to physiological maturational processes. Environmental toxins include exposure to illicit drugs and legal substances such as cigarettes, alcohol and inappropriate use of over-the-counter medication.

Psychological factors include increased capacity for self-reflective thinking and development of a more sophisticated sense of self. A more robust self-identity is related to the development of personal values with may include moral, political, sexual, religious or spiritual values as well as future educational and work aspirations. Much psychological development occurs within the context of the school environment.

To conclude this discussion on aetiology, it should be acknowledged that several factors are not development stage specific but rather are factors that are influential across developmental phases. The family's resources; financial, emotional and cultural, and social economic class (SEC) are influential developmental factors. Socioeconomic disadvantage and poverty have been linked to not only child and adolescent behaviour problems and conduct disorder but also more bio-behavioural processes such as the exposure of children to spoken and written language and the number of encouragements and discouragements given to the child during the early years. Note it is simplistic to ascribe causation to family SEC, rather this is a summary of a complex variety of constructs, for example may include parent mental health, parent availability, dislocation from extended family resources and access to other resources that enrich the child's development.

Biological effects can be influential across the lifespan such as some genetic factors, for example the presence of a genetic mutation seen with Velocardiofacial syndrome or the persistence of problems caused by anoxic brain damage at birth. Parental influence is also a persisting developmental effect. For example parents who have a coercive parenting style will continue to demonstrate this parenting style unless helped to do otherwise. In turn coercive parenting is related to the development of oppositional defiant disorder and later conduct disorder.

Finally, the child and family's culture must be considered in any aetiological formulation. Culture affects many of the determinants of health, as well as the construction of whether a given phenomenon is a health issue. For examples some cultures are more willing to acknowledge youth suicide. Whilst clearly effecting data and statistical analysis, at a personal level help seeking behavior for suicidal youth is likely to be effected by social views on this issue. Culture is often seen as a strong developmental continuity. However, for some countries in the developing world cultural change is rapid and has profound effects on children, an example being prolonged parental absence due to adults following employment opportunities in major cities.

14.2.5 Treatment

Pharmacotherapy

Prior to a discussion of pharmacotherapy it is prudent to discuss the decision-making process around the use of medication, especially given the rapid advances in this area and the array of medications now available. Whilst in some centers there is easy access to senior colleagues for advice, as a default strategy this is generally unsustainable and clearly does not work in regional hospitals or rural and remote settings. To this end practitioners need to be adept at accessing contemporary clinical practice guidelines from professional organizations (e.g., N.I.C.E.), Cochrane reviews, other published meta analyses and systematic reviews. Pharmacotherapy texts are often very informative, so too formularies that are often produced by government bodies; albeit care is required as some information can become out of date. The technology age has also made long distance communication available to many and so advice via email or phone can be obtained even if geographically remote. On-line discussion groups are also becoming more popular.

If these strategies do not provide the answer required then one should consider the conclusions of a seminal study in the area. Prior to accepting the findings of a seminal study the practitioner should determine whether the study is methodologically sound, has sufficient power, both genders and a range of ethnicities and social economic groups are included as participants thereby allowing generalization of findings into various practice settings. Finally, conclusions should be conservative in that they are consistent with the rigour of the methodology and strength of the analysis.

Various authors have published psychopharmacology practice advice relevant to children and adolescents. The over-arching principle is that medication prescription should only follow an adequate assessment and formulation. A broad formulation will determine whether there are ongoing causal or maintaining factors within the family system or local ecology. Many practitioners find the "predisposing, precipitating and perpetuating factor" heuristic helpful. An example being one should not prescribe medication for anxiety if the child is still being physically abused. In this case the treatment is to facilitate the provision of a safe environment. A prescribing generalisation is to start with a low dose. Child and parent compliance can be radically undermined by early adverse side-effects and so slowly increasing medication dose at the same time as predicting typical adverse events is prudent. Whenever possible dosage regimes should be dependant on the child's weight. There are adequate milligrams (drug) per kilogram (child weight) dosage schedules for stimulant medication, some atypical psychotics, tricyclic antidepressants such as Clomiprame for OCD and Sodium Valproate. Once a decision to prescribe is undertaken then the medication trial should continue, with regular monitoring, until an adequate dose has been trialed for an adequate period of time. Premature cessation creates uncertainty as to whether a certain medication is beneficial or not. If available and there are no financial constraints, new medications are preferable especially given their greater safety profile and fewer side-effects. Good prescribing needs to consider whether there are physical factors that influence the bioavailability of the medication such as concurrent liver or renal disease and in the patient with epilepsy some medications, especially anti-psychotic medication, can lower the fit threshold. Drug-drug interactions can occur, especially when drugs are combined which both affect these same neurotransmitter pathway.

When practicing child and adolescent psychiatry or behavioural paediatrics, there can be pressure from parents or teachers to increase medication dose beyond the usual parameters or too prescribe additional medications to obtain symptom control. This can be a serious problem in the overall management of the case. Family dysfunction including arguments between parents or the threat of school suspension is not a valid reason to increase the child's medication. There are persuasive research findings, for instance in the area of ADHD, that combining psychological interventions with medication is associated with lower medication dose. One assumes combined therapy can also decrease the number of medications required. Symptom deterioration is a reason to (a) review the diagnosis, (b) review barriers and maintaining factors, (c) look for new causal factors (d) review your therapeutic alliance with the child and family and (e) to consider comorbidity. The latter may be secondary to the original presentation, for instance a depressive illness in a teenager struggling with chronic anorexia nervosa. When these factors have been accounted for then increasing the dose or considering a second medication is reasonable. The prudent practitioner will also decide upon a small selection of medications with which they become very familiar with and prescribe preferentially. Use of a small number of medications allows greater knowledge of the typical dosage regime, side-effects and interaction profiles and also allows the practitioner to prepare and have ready access to patient information handouts.

Psychotherapy

Psychotherapy with children and adolescents can be divided into individual, family and group approaches. Individual therapies are usually either psychodynamically informed or a cognitive- behavioural intervention, often with variations of cognitive or behavioural interventions depending on the age of the child, cognition being treated or the experience and training of the psychiatrist. Key elements across types of psychotherapy include therapy designed to be appropriate to the developmental stage of the child, all therapy being delivered within a family construct (not just "family therapy") and the therapist being suitably trained and their work is related to a known theoretical framework.

Behaviour therapy is usually symptom focused where the symptom is a problematic behaviour. Therapy is often brief, may involve the parent as a "coach" and helps promote desired behaviours and eliminate the problem behaviour. Whilst initially in the clinic or hospital, behaviour therapy works well in the real-world, addressing actual difficult symptoms such as agoraphobia or social phobia. Therapy tends to be practical, "here and now" and there is little emphasis on cognitions or dynamic insights. An example of behaviour therapy is "flooding" the child with separation anxiety disorder by assisting the parents to take the child to school and then leaving the children with teaching staff. Or if the same is done in a more gradual fashion then this may be more akin to desensitization. Cognitive behavioural therapy (CBT) expands on behaviour therapy by adding interventions that identify problematic thoughts or cognitive schema and introduces practices that directly challenge unhelpful thoughts and replace them with more helpful cognitions. There is considerably variation within CBT as regards the extent to which therapy focuses on behaviour, on cognitions or even on the underlying patterns of thinking and relating which form the fertile ground from which symptomatic thoughts and behaviours may arise. CBT is active, often "now" orientated and relies on out of session work by the child, often with parent assistance. Home work is a feature of CBT. Some CBT interventions are manualised and this greatly aides

their formal research evaluation. Indeed the evidence base for many CBT programs is more robust than other forms of psychotherapy. There exist CBT packages for children who experience depression and different types of anxiety such as OCD, panic-agoraphobia and social phobia. It is perhaps the manualisaton, the growing evidence base and the relative brevity of these forms of therapy that may result in their rapidly increasing popularity over recent years.

Psychodynamic psychotherapy generally is longer term. While it is the existence of the presenting problem that is the stimulus for treatment, the therapy is generally more focused on helping the patient to gain insight, to understand the patterns in their thinking, feeling and relating which cause repeated difficulties and to be able to communicate in more healthy ways. Although the description of psychodynamic psychotherapy may resemble that of other therapies, for instance schema based cognitive behaviour therapy, it is marked out from these by its trade mark technology which is the focus on the way the patient relates to the therapist and to material from the patient's unconscious mind. The focus on the "underlying" may be problematic if the therapy does not seem sufficiently relevant to the presenting symptom, but does have the potential for personal growth and resilience should symptoms recur at a later time. Dynamic approaches vary across the child and adolescent span. At younger ages therapist employ more creative techniques such a drawing and play.

Indeed Art and Play Therapy are generally psycho-dynamically informed and require further training and supervision. Longer term strategies have great value especially for seriously abused children and youth who are often in crisis and cannot make use of the structure inherent to CBT and the motivation required. With these individuals psychodynamically informed support and containment can be very helpful. With improvement the focus of psychodynamic therapy can alter from support to more insight oriented techniques or incorporate elements of CBT. There are many schools of family therapy and there are many differences between these. What they have in common is a perspective which brings to the foreground, not the inner world of the child or adolescent (though for some schools this remains important), but the relationships, communication patterns and shared beliefs within the family and other social systems within which the patient lives and functions. The developmental life cycle perspective is as integral to understanding families as it is to thinking about individuals. Some presentations can best be understood in terms of difficulties in negotiating family life cycle stages e.g., teenager becoming more independent and eventually leaving home and what this means for other family members and relationships. A narrative approach to family therapy might explore the way the family members understand their difficulties and whether there are alternative understandings which might lead to new possibilities. Family counselling and psychoeducation is also part of the repertoire of family interventions, often to help families cope with presentations that may be primarily biological not family dynamic in origin, for instance assistance coping with the behaviour of an autistic child. Confusion may arise with family therapy in terms of who is the patient. Some families bringing an identified patient are comfortable with the idea that the whole family is the patient and that all in the family will need to change. Others find this an alien concept and feel blamed when family therapy is recommended for a problem which, to them, resides within one member. It may be helpful to explore this and to address the issue of family being helped to help one of its members versus family being treated as the patient.

Combined treatment

In the management of child and adolescent mental health presentations it is usual to begin with mono-therapy; usually in the form of one of the "talking" therapies. Across a range of approaches psychotherapy is not only helpful for symptom reduction but also enhancing resilience. Most treatment algorithms cite that for some conditions addition of a drug treatment can be beneficial. In this sense the medication is adjunctive to the primary psychotherapeutic interventions. For example addition of an SSRI medication to either Bulimia nervosa or OCD where psychological treatment alone produces insufficient benefit, is warranted and has an evidence base. Further, some studies, including those with ADHD, have concluded that combination of medication with psychotherapy decreases the ultimate dose of medication required. Combined treatments can also potentially lead to more rapid symptom reduction and be more cost effective.

15 Dementia, Delirium, and Psychiatric Symptoms Secondary to General Medical Conditions

In this chapter, we consider three related types of medical psychiatric disorders, usually accompanied by behavioral abnormalities: dementia, delirium, and neurobehavioral disorders due to general medical conditions. The common factor in these admittedly diverse conditions is a pathological alteration of brain structure and/or function, leading to abnormalities in cognition, affect, perception, or behavior. In the older U.S. literature, the term "organic brain syndrome" was often used to distinguish these conditions from so-called functional psychiatric disorders, such as schizophrenia or major depression. Indeed, the "organic" designation is retained in the ICD-10 classification (ICD-10, 1993).

In our view, however, the terms "organic" and "functional" suggest a false dichotomy. As we have learned more about the pathophysiology of common psychiatric disorders, such as schizophrenia or depression, the conceptual demarcation between these conditions and those discussed in the present chapter has become less distinct. For example, decreased metabolic function in frontal brain regions may be observed in both dementia and major depression, though the course and prognosis of these conditions differ markedly. Similarly, abnormalities in the cholinergic system may be present in both Alzheimer's Disease and schizophrenia (Raedler et al. 2007), notwithstanding the many differences between these disorders. Advanced neuroimaging techniques, genetic studies, as well as abnormal neurobiologic function in several animal models suggest receptor and circuit disturbances, even in the absence of traditional neurological abnormalities such as stroke or tumor. For all these reasons, we generally avoid the term "organic" in this chapter, but do use it when a particular study, author, or context justifies it.

The term "cognitive disorder" is often used to encompass delirium, dementia, and related conditions. This term appropriately emphasizes that a disturbance in memory, language, or attention is usually a cardinal feature of these disorders. However, the term "cognitive disorder" is far from ideal, since other aspects of consciousness, mood, and behavior may be strikingly abnormal in delirium, dementia, and related conditions. For example, the patient with frontal lobe dementia may show marked behavioral disinhibition, while the patient with Parkinson's Disease and dementia may show signs of major depression.

The disorders discussed in this chapter are seen in many health-care environments, and are by no means confined to psychiatric settings. For example, between 11-16% of inpatients on general medical units may experience delirium at some time during their admission (Levkoff et al. 1991). In skilled nursing facilities, at least 14 % of residents may suffer from some form of dementia (Sabbagh et al. 2003), with some studies finding that more than 50% of nursing home beds are occupied by patients with Alzheimer's Disease (Sadock & Sadock, 2007, p. 329). And while there are no reliable prevalence statistics for psychiatric symptoms due to

general medical conditions (GMCs), these disorders appear to be common in emergency department (ED) settings, where they often go undiagnosed. Indeed, in one study (Tintinalli et al. 1994) the chart was documented "medically clear" in 80% of ED patients in whom medical disease should have been identified.

Finally, a word about diagnostic systems: in most respects, there are more similarities than differences between the DSM-IV and ICD-10 classifications of the disorders discussed in this chapter; indeed, our discussion emphasizes common features rather than the specific criteria set forth in these two systems. However, when significant differences are clinically relevant, we will note them.

Dementia

Phenomenology (Characteristic Features of the Dementias)

Dementia may be broadly defined as a progressive, acquired impairment of cognitive function sufficient to cause functional decline, and occurring in a relatively normal ("clear") level of consciousness; i.e., in the absence of delirium (Sadock & Sadock, 2007; Apostolova & Cummings, 2008). We shall see, however, that there are some notable exceptions to this generalization, and that it is often more useful to define specific types of dementia. Global impairment of the intellect is a cardinal feature of dementia. More specifically, most dementia syndromes demonstrating the following neurobehavioral deficits:

- Memory impairment (either impaired ability to learn new information, or to recall previous information), usually evident for at least 6 months
- Deterioration in judgment, planning, and organizing (e.g., impaired shopping, cooking, handling money)
- Absence of "clouding of consciousness" for a period long enough to demonstrate decline in memory
- Decline in emotional control or motivation; or a change in social behavior (e.g., emotional lability, irritability, apathy, loss of social graces). DSM-IV specifically emphasizes a significant impairment in social and/or occupational functioning, as a result of the aforementioned deficits
- DSM-IV emphasizes one or more of the following: aphasia (language disturbance), apraxia (impaired ability to carry out motor activity despite intact motor function), agnosia (failure to recognize objects despite normal sensory function); and disturbance in executive functioning (planning, organizing, sequencing, abstracting). In partial contrast, ICD-10 regards these as essentially supportive findings for diagnosis of dementia.

The epidemiology, clinical features, and pathogenesis of dementia vary considerably, depending on the subtype; for example, dementia of the Alzheimer type (DAT), Vascular Dementia, Lewy Body Dementia, etc. Nevertheless, it is common to encounter elderly patients in the clinical or nursing home setting who carry only the syndromic diagnosis of "dementia" (Jacobson et al. 2007). It is worth noting that not all definitions of dementia require memory impairment as a diagnostic criterion; indeed, some patients with frontotemporal dementia (FTD) may be severely affected with behavioral disturbances before memory impairment is prominent (Jacobson et al. 2007). Dementia must be distinguished from so-called mild cognitive impairment (MCI), which appears to represent an intermediate stage between

normal aging and dementia (Apostolova & Cummings, 2008). Unlike those with dementia, MCI patients do not show significant impairment in activities of daily living.

Epidemiology of the Dementias

Dementia of some type may afflict as many as 28 million individuals world-wide, with direct costs for care estimated at 156 billion U.S. dollars (Wimo et al. 2006). Of the total number of demented individuals worldwide, the largest proportion (5.2 million, or 18.5%) lives in China (Wimo et al. 2006). If one groups all dementias together, the estimated prevalence is about 5% in the general population older than age 65, and 30% in those older than age 85 (Sadock and Sadock, 2007 p. 329). Findings on racial variations in dementia are somewhat equivocal, but most studies have reported higher frequencies of dementia among nonwhite persons (Husaini et al. 2003). Disproportionately high rates of dementia among African-Americans may be due, in part, to a higher prevalence of both hypertension and stroke among elderly African-Americans. Women generally have higher rates of dementia than men, largely because women live longer (Husaini et al. 2003). However, vascular dementia appears to be more common in men.

Dementia of the Alzheimer's Type (DAT, "Alzheimer's Disease") is by far the most common type of dementia, making up roughly 35%-60% of cases worldwide (Mendez & Cummings, 2003; Sadock and Sadock, 2007, p. 329). The wide range of these figures is due in part to some controversy over the classification of Lewy Body Dementia (LBD); i.e., if LBD is considered a variant form of DAT (Sadock and Sadock, 2007, p. 329), the prevalence figure for DAT tends toward the higher end of the range. Many geriatric psychiatrists consider LBD to be the second most prevalent dementia subtype ("tied" with mixed vascular dementia/DAT), with a prevalence of about 15%. About 10% of dementias are said to be represent pure vascular dementia, while another 5% represent fronto-temporal dementia (Mendez and Cummings, 2003; Jacobson et al. 2007). Some data suggest that the DAT/vascular dementia ratio is comparatively higher in South America and lower in Asia (Lopes & Bottino, 2002), though the reasons for these trends are not clear. Miscellaneous causes of dementia—including cases due to Huntington's Disease, Creutzfeld-Jakob Disease, Parkinson's, HIV infection, and other conditions—probably constitute fewer than 5% of the total.

That said, there is a paucity of autopsy-based studies of dementia prevalence, which would presumably be more accurate than those based on clinical diagnosis alone. In one of the few such studies (Fu et al. 2004), 202 demented patients underwent brain-only autopsies, and the following types of dementia were found: 129 (63.8%) cases showed changes of severe Alzheimer disease; 21 (10.4%) showed combined neuropathologic abnormalities (Alzheimer disease plus another type of lesion, such as significant ischemic infarcts or diffuse Lewy body disease), 12 (5.9%) cases of relatively pure ischemic vascular dementia, 13 (6.4%) cases of diffuse Lewy body disease, and 8 (4.0%) cases of frontotemporal dementia. The remaining 19 (9.4%) patients showed various neuropathologic diagnoses, including normal pressure hydrocephalus and progressive supranuclear palsy. Notably, the authors concluded that, had these diagnoses been known ante mortem, the clinical care of the patients might well have been different (Fu et al. 2004).

Clinical Features of Dementia Subtypes

Cortical vs. subcortical distinction

The older literature on dementia often describes two broad subtypes that encompass many of the more pathologically-specific types of dementia. Though the distinction between so-called cortical and subcortical dementias is controversial, it remains a useful conceptual tool in preparation for understanding more specific forms of dementia (Turner et al. 2002). Although there is no specific neuropsychological pattern in subcortical dementia, this group of disorders is generally characterized by cognitive slowness, concomitant motor abnormalities, and a relatively low frequency of aphasias and apraxias, compared with Alzheimer-type dementia (Turner et al. 2002). The principal differences between cortical and subcortical dementias are summarized in Table 1. It is important to note that some conditions—such as multiple small strokes and certain toxic-metabolic disorders—produce symptoms of both cortical and subcortical dysfunction (Cummings, 1985). Furthermore, the cortical/subcortical distinction has become less useful as our understanding of specific dementia syndromes has increased (Turner et al. 2002). Indeed, Lerner and Riley (2008) have pointed out that the dementias of Huntington's and Parkinson's Disease—two putative "subcortical" dementias—are as different from each other as they are from Alzheimer's Disease, the classic "cortical" dementia. Furthermore, these authors note that "...the pathological basis for dementia in (Parkinson's Disease) is now known to lie in the cerebral cortex...effectively rendering its designation as a "subcortical" dementia untenable." (p. 908). In short—though useful as a rough, first-pass approximation—the designations "cortical" and "subcortical" are likely to be modified with more specific pathoanatomical and descriptive assessments.

Table 1: Putative Differences in Cortical vs. Subcortical Dementias

	CORTICAL DEMENTIAS	**SUBCORTICAL DEMENTIAS**
Locus of pathology	Mainly frontal, temporal lobes, hippocampus	Mainly basal ganglia, brainstem nuclei, cerebellum, periventricular white matter
Nature of pathology	Neocortical atrophy, neuronal degeneration; plaques, neurofibrillary tangles	Depends on specific disorder; in Parkinson's loss of DA-containing cells in substantia nigra, ventral tegmental area; in Huntington's, cellular loss/atrophy in caudate, putamen
Cognition/executive function	Amnesia, Dyscalculia, dysphasia, dyspraxia, agnosia prominent; visuospatial deficits, poor abstraction	Forgetfulness, psychomotor retardation, slowed thinking (bradyphrenia) independent of motor slowness, poor strategic skills

	CORTICAL DEMENTIAS	SUBCORTICAL DEMENTIAS
Motor function/posture	Minimal to moderate motor dysfunction (e.g., mild EPS) until late in course; posture often upright	EPS, chorea, dystonia, tremor more common; posture often stooped; wide-based gait
Speech	Usually normal until late in course	Dysarthria common
Mood/affect/personality	Often apathetic/indifferent; depression, dysphoria are common but mood may be euthymic	Depression, dysphoria, agitation more likely than apathy; euthymia rare

Cummings, 1985; Turner et al. 2002; Sadock & Sadock, 2007; Apostolova & Cummings, 2008.

- Dementia of the Alzheimer Type (DAT)

Case vignette: Mrs. A, a 91-year-old widowed Caucasian woman in good general health, was seen by her family physician for complaints of "forgetting things a lot lately." Mrs. A's daughter, who often helped her mother with household chores, had noticed a change in her mother's thinking and behavior over the past two years. "Mom used to be sharp as a tack and never forgot a thing," she reported. "Nowadays, she has trouble remembering even simple things, like turning off the stove, or in what room she keeps all her bills and papers. The other day, I found that she had left the bath running for over an hour, and it flooded the whole upstairs. Sometimes, Mom confuses me with her sister, who died over twenty years ago. When I try to explain who I am, Mom sometimes gets kind of irritable with me, and says I'm trying to confuse her." There was no history suggestive of stroke, sudden change in mental status, or loss of gross motor or sensory function. On mental status exam, the patient was pleasant, socially appropriate, and in no acute distress. She was oriented to the year, but not to month, day, or date. She recalled only one word item after three minutes. She could not remember the name of the two most recent U.S. Presidents, but was able to speak knowledgeably about the Presidents during the U.S. Great Depression (1929-1941). When asked to name three objects on the physician's desk (stapler, paper clip, and calendar), she named them as "stapler, paper grip, and day book." A provisional diagnosis of "dementia, probably of the Alzheimer's type" was made by the physician.

AS the vignette suggests, DAT (Alzheimer's Disease) is characterized most saliently by a gradual onset and progression of cognitive decline. Frank signs and symptoms of DAT often follow a prodromal stage of mild memory impairment that does not markedly interfere with activities of daily living. With disease progression, the patient shows more global cognitive decline, with disturbance in language, visuospatial skills, executive functioning, and social interaction. Typical of progressive DAT is a transcortical sensory aphasia, in which the patient shows fluent word output and preserved ability to repeat spoken language, but impaired speech comprehension (Apostolova & Cummings, 2008). With further progression of DAT, the patient shows impaired judgment and reduced ability to carry out activities of daily living. Disturbances in sleep-wake cycle or appetite often ensue. Although depression is often considered a hallmark of subcortical dementias, it is actually a common feature in DAT. However, only about half of patients with depression/dysphoria in DAT meet full criteria for

major depression (Apostolova & Cummings, 2008). Irritability, agitation (including pacing, "fidgeting" or verbal outbursts) and psychotic features (such as visual hallucinations and delusions of having been robbed) are also common in DAT, and impose great emotional burdens on the patient's family and caregivers. Patients with early-onset DAT (see under Pathogenesis) may show atypical features, such as prominent aphasia, myoclonic jerks, emotional lability, or obsessive-compulsive symptoms (Apostolova & Cummings, 2008).

- Vascular Dementias

Vascular dementia (VaD) is considered the third leading cause of dementia in the elderly, after DAT and Dementia with Lewy Bodies (Apostolova & Cummings, 2008). However, some experts regard VaD as a heterogeneous syndrome, rather than a distinct disorder, in which the underlying cause is some type of cerebrovascular disease and the end result is dementia (Wright, 2007). Several subtypes of VaD are recognized. Multi-infarct dementia (MID)—the older term for VaD—involves multiple, relatively large infarctions, usually due to recurrent cerebral emboli originating from the heart, thromboembolic events, or atherosclerotic plaques. Single, strategically-placed infarct; lacunar state; and Binswanger's Disease (subcortical arteriosclerotic encephalopathy (SAE) due to arteriosclerotic narrowing of deep penetrating white matter arterioles) are also considered VaD subtypes (see below).

In partial contrast to DAT, vascular dementia often shows a subcortical pattern, with prominent psychomotor slowing, executive dysfunction, and mood changes. Speech difficulties (dysarthria) are common. Compared with DAT, memory deficits in VaD are more often related to retrieval than to initial encoding of memories; for example, the patient with VaD may be unable spontaneously to "retrieve" the name of a recently specified object (such as "chair"), but can do so if provided a clue ("It rhymes with hair"). In contrast to the course of DAT, VaD of the multi infarct variety may have a "stuttering" course, with a stepwise progression of cognitive deterioration, often accompanied by lateralizing neurological deficits (Sadock & Sadock, 2007). SAE often has an insidious course that may be temporally difficult to distinguish from DAT. The neurological findings of multi-infarct dementia may include focal findings such as weakness, spasticity, rigidity, and extensor plantar reflex (positive Babinski sign). Compared with DAT, VaD has a higher incidence and greater severity of new-onset depression, especially in older individuals; this is sometimes referred to as "vascular depression." Psychosis is also relatively common in VaD.

- Lewy Body Dementia

Barely recognized only 20 years ago, Dementia with Lewy Bodies (DLB) is now believed to be the second most prevalent dementia of old age, accounting for some 15-20% of cases (McKeith et al. 1996). Compared with DAT, memory impairment in DLB is less pronounced, but cognitive fluctuations are severe. Variability in the patient's attention, alertness, and level of consciousness may reach the proportions of frank delirium (see below, Delirium). Recurrent visual hallucinations are also one of the hallmarks of DLB. DLB shares features with the dementia of Parkinson's Disease (PD), and diagnosis is conventionally determined by the temporal pattern of motor symptoms: if these precede cognitive decline by more than 12 months, PD is diagnosed, whereas motor symptoms occurring within a year of cognitive decline would be diagnosed as DLB (Apostolova & Cummings, 2008). Bradykinesia, rigidity, resting tremor, and gait disturbance are commonly seen in DLB, but cases of DLB without extrapyramidal symptoms are reported. Other clues to the presence of DLB include a history of falls or syncopal episodes; REM (rapid eye movement) sleep behavior disorder (such as

violent behaviors during REM sleep); and extreme sensitivity to neuroleptics and atypical antipsychotics (Apostolova & Cummings, 2008; Jacobson et al. 2007—see under Treatment).

- Fronto-temporal dementia

Fronto-temporal dementia (FTD) is actually a group of three related disorders, involving focal atrophy of the frontal and/or temporal lobes, accompanied by characteristic neurobehavioral impairments (Apostolova & Cummings, 2008). So-called Frontal Variant FTD is also known as Pick's Disease and makes up the majority of FTD cases. (Primary Progressive Aphasia and Semantic Dementia are less common FTD variants, and will not be discussed here).

Patients with Frontal Variant FTD typically do not complain of cognitive problems to the same extent as patients with DAT; rather, they show insidious but profound alterations in personality, social skills, and impulse control. However, neuropsychological testing does reveal deficits in verbal fluency, abstract thinking and planning, and verbal memory, often with sparing of visual memory. Compared to DAT patients, those with FTD usually have more mood disturbance, behavioral disinhibition, and abnormal motor behavior. Curiously, nearly half of all FTD patients—two years after diagnosis--will show one or more stereotyped or obsessive-compulsive behaviors. These may include hand clapping, hoarding, and repetitive or ritualistic behaviors (Mendez & Perryman, 2002; Apostolova & Cummings, 2008). Twenty per cent of FTD patients may develop a form of Kluver-Bucy Syndrome (hyperorality, hypersexuality, and abnormal exploratory behavior) two years after diagnosis (Mendez & Perryman, 2002).

Case vignette: Mr. J. was a 57-year-old married white male, with a two-year history of marked "change in personality", according to his wife. "It's like night and day," she told the neurologist, "compared to the way Fred used to be. He was the kindest, gentlest man I ever knew. Now, it's like Jekyll and Hyde—I'm afraid to look at him cross-eyed, for fear he will scream at me, or worse." Mr. J. had always been a very empathic individual, but now seemed unconcerned with the wishes or needs of others. His hygiene and personal grooming had deteriorated over the past year, and he had begun to engage in bizarre rituals every morning; for example, counting to 100 before getting out of bed, then eating exactly six large muffins, without saying a word to his wife. Most of the time, Mr. J. seemed "flat" and apathetic; however, when his wife questioned any of his actions, he would shout at her or throw some object across the room. A neurological evaluation found evidence of significant frontal lobe dysfunction and positive "grasp reflex", but was otherwise within normal limits.

- Miscellaneous Dementia Syndromes

In addition to the aforementioned types of dementia, about 5% of patients will have dementia due to miscellaneous causes, including Huntington's Disease, Creutzfeld-Jakob Disease, Parkinson's Disease, HIV infection, and other conditions. Huntington's Disease (HD)—an autosomal dominantly-transmitted, progressive disorder—has its peak onset in the fourth and fifth decade, though a smaller peak occurs in the 20s. The classic presentation for HD is a combination of chorea and dementia, in the setting of a positive family history; however, the earliest presentation may be with affective or psychotic symptons (Lerner & Riley, 2008). A "tendency toward suicide" in HD was recognized by Huntington himself, and suicidal ideation may be the presenting problem. Creutzfeld-Jakob Disease (CJD) is caused by an abnormal protein called a prion, and typically presents as a rapidly-progressive dementia, accompanied by ataxia and multi-focal myoclonic jerks. A third of patients with CJD show a prodrome of fatigue, headache, insomnia, malaise, or depression (Apostolova

& Cummings, 2008). Dementia due to Parkinson's Disease (PD) occurs in roughly 30% of patients with PD, with a larger percentage afflicted as age increases (Lerner & Riley, 2008). However, cognitive symptoms can occur at any stage of PD, and are often characterized by slowed mentation (bradyphrenia), impaired visuo-spatial skills (such as facial recognition and operating objects in space) and executive dysfunction. Affective disturbance—especially depression—is very common in PD, and may be present in over 60% of cases. Anxiety is also commonly seen in PD, although less frequently than depression (Lerner & Riley, 2008). Psychosis is also encountered in PD, usually related to dopaminergic effects of anti-Parkinsonian medication (Lerner & Riley, 2008).

Cognitive deficits associated with HIV infection are considered part of a continuum, known as HIV-1-associated cognitive-motor complex (HCMC). Frank HIV dementia is the most serious form of HCMC, and occurs in roughly 30% of HIV-infected individuals (Fernandez & Tan, 2008). The early clinical picture in HCMC is usually characterized by subcortical features (see Table 1), including reduced information processing speed; motor slowing or dyscoordination; and depressed mood. However, as the illness progresses, more classically "cortical" features may develop, including aphasia, agnosia, apraxia, and frontal lobe symptoms (Fernandez & Tan, 2008). Behavioral disinhibition, mania, and psychotic features are often found in the later stages of HIV-associated dementia.

Assessment and Diagnostic Testing

In addition to obvious abnormalities in the mental status exam, the patient with dementia may show a variety of deficits on more sophisticated screening instruments and neuropsychological assessments, and on neuroimaging studies.

- Prototypical mental status findings in dementia

Considering the diverse subtypes of dementias, it is difficult to generalize about findings on mental status exam. Furthermore, the clinician must proceed with the caveat that a patient cannot be diagnosed with dementia, in the presence of active delirium (see Delirium, section). Nonetheless, if we "average out" the differences between cortical and subcortical dementia presentations, the following mental status exam could be considered typical of the patient with moderately severe dementia:

The patient appears alert, but apathetic and somewhat agitated, and is seen to be twisting her fingers through her hair. Her speech is fluent and well-articulated, but she uses many long, meaningless phrases (such as, "The thing of it is, you see, I need the thing to be, you know, whatever."). She is oriented to year, but not the month or day. She recalls only 1 of three named items, after a three minute interval of distraction. She cannot remember the names of the college from which she graduated, and gave an incorrect response when asked, "Who is the current president of the U.S.?" When shown a picture of a cup, she calls it a "vase", and identifies the examiner's stethoscope as a "hearing aid." She is able to subtract 10 from 100 correctly, but cannot do serial 10's accurately ("90, 85, 75, 65, 50, 40. . . "). She produces a poorly-constructed drawing when asked to copy a cube, and her drawing of a clock reading "ten past two" was incorrect (with the big hand placed at the "10" position). When asked to interpret the proverb, "The early bird catches the worm," her response is very concrete ("The bird that gets up early will catch the worm."). When asked if she has any particular fears lately, she replies, "I don't know what the neighbors think of me, but I know they steal from my bedroom" (Spitzer et al. 1994).

- Screening instruments and neuropsychological assessments

The most widely-used screening instrument for dementia is the Mini-Mental State Exam (MMSE) developed by Folstein (Folstein et al. 1975), an 11-item test that evaluates orientation, registration, attention and calculation, recall, and language. The maximum score on the MMSE is 30 and—depending on age and education--a score of 28 or higher is usually considered "normal." A "low normal" score (24 or higher) appears to predict development of dementia after three years (Braekhus et al. 1995). The MMSE does not specifically examine executive cognitive function. An expanded version of the MMSE (the 3MS) does include some executive function items, and may be more sensitive, specific and predictive of functional outcome than the MMSE (Grace et al. 1995). Neither the MMSE nor the 3MS is ideally suited to detecting features of "milder" or subcortical dementia, or detecting impairments in social or operational functioning. For HIV-related dementia, the HIV dementia scale or the Mental Alternation Test may be better alternatives (van Harten et al. 2004; Billick et al. 2001). More complete neuropsychological assessment of dementia usually includes use of the Wechsler Adult Intelligence Scale-III (WAIS-III), the Wechsler Memory Scale (WMS), the Rey Complex Figure, and Trail Making Test (Howieson & Lezak, 2008), among others. These ancillary tests may be helpful in pinpointing specific functional impairments and their neuroanatomical correlates.

- Neuroimaging studies

Neither the ICD-10 nor the DSM-IV criteria for dementia require any corroborative evidence obtained from neuroimaging studies. Nevertheless, neuroimaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET) may be helpful in clarifying diagnosis and ruling out other types of brain disease, such as normal pressure hydrocephalus. Indeed, the American Academy of Neurology recommends a non-contrast structural image (CT or MRI) in the initial evaluation of cognitive impairment (Apostolova & Cummings, 2008). With DAT, global cerebral atrophy, especially in mesial temporal and parietal regions, is the usual finding on CT or MRI. On PET or SPECT (single-photon emission computed tomography), DAT patients usually show bilateral hypometabolism in mesial temporal and parietal regions. Recently, a novel radio-labeled PET imaging agent, 18F-AV-45, has been developed, and may eventually provide a practical approach for routine brain imaging for Alzheimer's Disease (Alzheimer's Association, 2008).

In dementia with Lewy Bodies (DLB), bilateral parietal and occipital hypoperfusion is seen. The latter helps distinguish DLB from DAT, and may explain the high prevalence of visual hallucinations in DLB. Structural imaging (CT, MRI) is not helpful in diagnosing DLB (Lerner & Riley, p. 919). In frontotemporal dementia (FTD), the expected hypometabolism is seen in frontotemporal regions, using PET scanning (Apostolova & Cummings, 2008). Structural imaging (such as MRI) shows distinct profiles for the three main subtypes of FTD, though some degree of frontal and/or temporal lobe involvement is seen in all three subtypes.

In vascular dementia, both CT and especially MRI can be useful in defining cortical and white matter abnormalities. In multi-infract or lacunar states, evidence of prior infarct can be seen. In SAE, periventricular white matter abnormalities can frequently be seen, although limited periventricular abnormatilies just anterior or proximal to the lateral ventricle can also be seen in normal aging. Periventricular abnormalities of greater size or distance from

the ventricles, or extending into the centrum semiovale, are more likely to represent evidence of clinically significant disease.

- Investigational Biomarkers

Given the uncertainties of early dementia diagnosis, there has been great interest in a "blood test" or other valid biomarker for DAT, the most common type of dementia. Recently, for example, researchers in Germany found differences in levels of CD-69, a protein involved in white blood cell growth and production, in normal subjects versus those with DAT or Parkinson's-related dementia (Alzheimer's Association, 2008). Irish researchers have focused on the enzyme beta-secretase (BACE1) activity in the brain. (BACE1 is one of two enzymes involved in the pathological processing of amyloid precursor protein (APP)—see below, under Pathogenesis). High levels of BACE1 in the spinal fluid appear to be correlated with development of DAT. At present, these remain promising, but only investigational, techniques (Alzheimer's Association, 2008).

Pathogenesis of Dementias

- Biogenetic determinants and pathophysiology

Dementia of the Alzheimer Type

From the biogenetic standpoint, Alzheimer's Disease (DAT) appears to be of two main types: late-onset (sporadic) and early-onset. When DAT begins after age 65 (late onset), its mode of inheritance appears to involve a constellation of genes, probably influenced by epigenetic factors (i.e., influences that do not change DNA sequence) such as diet and exercise. However, increasing age is the most important risk factor, with rates of DAT rising to 40% in those 85 years or older. Increasing age acts synergistically with the apolipoprotein E (APOE) gene polymorphism on chromosome 19. The APOE gene takes three major forms (alleles), termed ApoE2, ApoE3, and ApoE4. APOE4 (E4) greatly increases the likelihood of late-onset DAT; i.e., individuals with two E4 genes develop DAT eight times more frequently than do those with no E4 gene. (Sadock and Sadock, 2007 p. 330; Apostolova & Cummings, 2008). It appears that E4 promotes aggregation of amyloid ? (A?), which leads to a variety of pathological changes in brain tissue (see below).

In early-onset DAT, instead of—or possibly in addition to—APOE4, three autosomal dominant mutations appear to be important: the APP gene mutation on chromosome 21; the presenilin-1-gene mutation on chromosome 14; and the presenilin-2 gene mutation on chromosome 1. As noted above, early-onset DAT may be associated with atypical features, as well as shorter survival time (Apostolova & Cummings, 2008).

The classic pathological findings in DAT is the presence of senile plaques, neurofibrillary tangles, neuronal and synaptic loss, and granulovascular degeneration of neurons (Sadock & Sadock, 2007, p. 330). The pathophysiology of DAT is integrally related to the over-production or accumulation of amyloid ? (A?). The "amyloid cascade hypothesis" of DAT posits that abnormal enzymatic processing of beta-amyloid precursor protein (?APP) leads to overproduction of neurotoxic A? peptides. These abnormal peptides polymerize (form chains) and "clump together", forming several types of destructive, extracellular inclusion bodies called plaques. The first plaques appear in temporal-occipital association

regions in patients with DAT. In addition, DAT may involve abnormal phosphorylation of a structural protein called tau, which is involved in microtubulular transport—the intracellular "highway system" that transports vital constituents within neurons (Apostolova & Cummings, 2008). In DAT, hyper-phosphorylated tau forms distructive intracellular inclusions called neurofibrillary tangles (NFTs). Together, these plaques and tangles "choke off" normal neuronal function and neurotransmitter production in DAT, particularly affecting the production of acetylcholine (ACh) and norepinephrine. Degeneration of cholinergic neurons is present in the nucleus basalis of Meynert in persons with DAT, and low brain levels of ACh and choline acetyltransferase are also found. Cholinergic deficits provide the rationale for use of cholinesterase inhibitors in the treatment of DAT (see below, Treatment). In addition, overactivation of NMDA receptors by the excitatory neurotransmitter, glutamate, is believed to play a role in DAT, and is the basis for one pharmacological treatment (see below re: memantine). Recently, it was discovered that elevated serum levels of amyloid ? are associated with reduced cognitive function even in healthy older adults, similar to patterns observed in early DAT (Gunstad et al. 2008).

Vascular Dementia VaD is caused by cumulative ischemic or hemorrhagic brain damage, usually secondary to cerebrovascular and cardiovascular pathology, and is often seen in association with hypertension, diabetes and hyperlipidemia (Apostolova & Cummings, 2008). There are somewhat conflicting data regarding the contribution of the ApoE gene to the pathogenesis of VaD, but any such contribution appears smaller than that in DAT (Higuchi et al. 1996).

Multi-infarct dementia (MID)—the older term for VaD—usually involves infarcts in the territory of the middle cerebral artery and surrounding ("watershed") regions. The middle cerebral artery is the largest cerebral artery and is the vessel most commonly affected by cerebrovascular accident. It supplies most of the outer convex brain surface, nearly all the basal ganglia, and the posterior and anterior internal capsules (Slater, 2008). In VaD, infarcts are also seen in the basal ganglia and periventricular white matter.

Subacute Arteriosclerotic Encephalopathy (SAE) and Lacunar state both involve the small vessels of the brain. SAE is caused by thickening and narrowing (arteriosclerosis) of arteries that feed subcortical areas of the brain. SAE produces widespread, microscopic areas of damage to the deep layers of white matter. (NINDS, 2008). Lacunar state (lacunar disease) is due to occlusion of small, penetrating cerebral arteries, leading to extremely small but deep infarctions (lacunes). Sometimes, these lacunes are so small as to produce no obvious deficits, or only pure motor or sensory deficits (Robinson & Starkstein, p. 707). Lacunar state is often associated with hypertension and/or diabetes. The cavitary lesions (lacunae) characteristic of this condition are often found in the internal capsule, deep grey matter nuclei, and white matter.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a rare, hereditary type of VaD that affects small blood vessels in the brain. An abnormality in the muscle cells surrounding these blood vessels gradually destroys the blood vessel cells. This may lead to migraines, emotional disturbance, stroke-like episodes, dementia, and other impairments (CADASIL Foundation, 2008). CADASIL involves mutations of the Notch 3 gene on chromosome 19 (Joutel et al. 1996). There are also a growing number of genetically uncharacterized but familial small vessel diseases (Low et al. 2007).

Dementia with Lewy Bodies (DLB) DLB does exist in genetic forms, including some autosomal dominant forms (Lerner & Riley, p. 919). There is significant pathophysiological overlap between DLB and Parkinson's Disease (PD), on the one hand; and DLB and SDAT, on the other. Thus, alpha-synuclein is a protein that appears to modulate synaptic transmission, and constitutes the major component of Lewy bodies. These structures are the pathological hallmark of both PD and DLB, whether of a sporadic or familial origin (Lerner & Riley, p. 914).

There is considerable overlap between DLB and DAT. For example, neuritic plaques and neurofibrillary tangles are seen in autopsy studies of both DAT and DLB, though fewer neurofibrillary tangles are found in DLB (Samuel et al. 1997). Moreover, amyloid ? (A?) pathology—one of the hallmarks of DAT—is often seen in DLB. Indeed, there is an interesting synergy between pathophysiological elements of DLB and DAT. For example, alpha- synuclein is a potent inducer of tau fibrillization, while A? has been shown to promote Lewy body pathology in animal models (Giasson et al. 2003; Masliah et al. 2001).

Fronto-temporal dementia

There appears to be a strong genetic loading in FTD. About 40% of FTD patients have a family history of a similar disorder in close relatives, and in the vast majority of cases, there is an autosomal dominant inheritance pattern. Autosomal dominant mutations in the tau gene on chromosome 17 have been discovered in FTD, and—like DAT-- FTD is generally considered a "tauopathy." However, "tau-negative" forms of FTD have been described, including one form that often presents with concomitant amyotrophic lateral sclerosis (ALS) (Apostolova & Cummings, 2008; Lantos & Cairns, 2001).

Pick's Disease (frontal variant FTD) produces striking frontal, temporal, or combined (fronto-temporal) atrophy. Microscopically, the hallmark are spherical, tau-based inclusion bodies, termed Pick's bodies, which may be seen in neurons and glial cells. Neuronal loss and swelling are also commonly seen in Pick's Disease. In tau-negative forms of FTD, neuronal loss, gliosis, and microvacuolation are the sole microscopic findings.

- Ethno-cultural and racial factors in dementia

Ethnic, cultural, and racial factors play a role in the assessment of dementia and, to some extent, on its course and outcome. For example, most diagnostic tests for dementia are based on cognitive assessments not yet validated for various ethnic groups. Moreover, emigration of some ethnic groups may affect dementia prevalence, as demonstrated by higher rates of dementia among Japanese-Americans than among Japanese cohorts in Japan (Iliffe & Manthorpe, 2004). Ethnic and cultural factors may also affect caregiver attitudes and behavior. For example, Latina dementia caregivers may delay institutionalization significantly longer than female Caucasian caregivers, perhaps reflecting more tolerant Latino cultural attitudes toward caregiving (Mausbach et al. 2004). Similarly, Shaw et al. (1997) found lower rates of depressive symptoms in Chinese, as compared with American, caregivers of demented patients, possibly reflecting greater acceptance of traditional family roles among the Chinese subjects. Finally, ethnicity and race may play a role even in the symptomatic expression of dementia, with different ethnic and racial groups showing varying rates of aggressive behaviors, wandering, and hallucinations (Sink et al. 2004).

Treatment of Dementias

Pharmacotherapy

By far the most experience with pharmacotherapy has been in patients with DAT, and our discussion necessarily focuses on this condition. The mainstay of drug therapy in dementia is a group of agents called cholinesterase inhibitors (CIs), including donepezil, galantamine, and rivastigmine. (Another CI, tacrine, is rarely used nowadays in most industrialized countries, owing to its hepatotoxic effects). Comprehensive discussion of these agents may be found in Jacobson et al. 2007. All CIs act to inhibit the enzyme acetylcholinesterase, which metabolizes the neurotransmitter, acetylcholine. Rivastigmine also inhibits butyrylcholinesterase, and galantamine is an allosteric modifier of the nicotinic acetylcholine receptor. There is no convincing, randomized, controlled evidence showing any one of these drugs as markedly superior to the others. Indeed, the efficacy of this group of agents appears to be modest-to-moderate, with most studies of DAT finding that the CIs mainly slow the rate of cognitive decline and/or delay nursing home placement. One meta-analysis of 13 randomized, double blind, placebo controlled trials demonstrated that 6-12 months of treatment with donepezil, galantamine or rivastigmine in mild, moderate or severe DAT produced about a 3 point drop in scores on the 70-point ADAS-Cog Scale. Benefits were also seen on measures of activities of daily living and behavior. But as the authors note, "none of these treatment effects (is) large." (Birks, 2006). The other drug used in most countries for DAT is memantine, which blocks the action of glutamate at the NMDA receptor, under conditions of excessive glutamate activity (Jacobson et al. 2007). This is thought to slow neurodegeneration in DAT, and there is evidence of memantine's benefits in moderate-to-severe DAT. In some instances, memantine may be combined with one of the CIs, but long-term data on outcome are few.

Although atypical antipsychotics are often used—and sometimes, overused—in patients with DAT, they are not without risk in dementia-prone populations, particularly when vascular risk factors are present. In the U.S., the Food & Drug Administration (FDA) issued, in June 2008, an advisory to physicians, stating the following (FDA, Alert, 6/16/08):

- Elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic drugs are at an increased risk of death.
- Antipsychotic drugs are not approved for the treatment of dementia-related psychosis. Furthermore, there is no approved drug for the treatment of dementia-related psychosis. Healthcare professionals should consider other management options.
- Physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss this risk of increased mortality with their patients, patients' families, and caregivers.

Notwithstanding these serious concerns, some patients with DAT and psychotic features and/or severe behavioral disturbance (e.g., extreme agitation or aggressive violence) may require and benefit from low doses of atypical antipsychotics; e.g., risperidone 0.5 mg/day or olanzapine 5 mg/day (Alexopoulos et al. 2004). However, attempts at behavioral

modification (see below) and alternative therapies (such as the SSRI citalopram) should be considered (Pollock et al. 2007). As a recent review by Ellison (2008) put it:

"...several of the atypical antipsychotics remain reasonable choices when used in patients whose vascular risk factors do not outweigh their behavioral treatment needs. The atypical antipsychotics have not been proved to control agitation over an extended period of time and should be used at the lowest effective doses and for the shortest interval necessary, with sufficient psychoeducation and disclosure of risks to caregivers and relatives."

Treatment of vascular dementia (VaD) should first focus on mitigation of known risk factors, such as hypertension, diabetes, atrial fibrillation, and hyperlipidemia. Studies regarding use of CIs for vascular dementia are plagued by methodological problems, such as inclusion of those whose dementia probably involves some DAT-type pathology and cholinergic system dysfunction; nonetheless, there is modest and growing evidence that the CIs may be helpful in subgroups of patients with VaD. Similarly, Dementia with Lewy Bodies (DLB) also involves reduction of brain acetylcholine—perhaps surpassing those seen in DAT--and the CIs may sometimes be useful in DLB (Jacobson et al. 2007). Patients with DLB are exquisitely sensitive to the extrapyramidal side effects of antipsychotics, and both typical and atypical agents (with the possible exception of clozapine) are generally to be avoided in DLB patients.

Psychosocial and behavioral interventions

Whenever possible, the clinician should initiate non-pharmacological interventions when managing behavioral disturbances in patients with dementia. Such behavioral approaches are aimed at ameliorating physical, environmental and psychosocial stressors that may lead to agitation, pacing, aggression, and related behavioral disturbances (Salzman et al. 2008). For example, dysfunctional verbal and physical behaviors—such as repetitive shouting, pacing, punching, etc.—may reflect unrecognized pain, loneliness, depression, boredom, or other social stressors. A variety of behavioral interventions may be helpful in this context; e.g., structured socialization, "pet therapy," viewing family videotapes, and training programs for family caregivers. It is also important to review the patient's medical status and medications, since adverse drug effects or interactions may sometimes contribute to confusion and agitation (Jacobson et al. 2007; Salzman et al. 2008). There are relatively few well-controlled studies of non-pharmacological interventions in dementia; nevertheless, a number of promising investigational approaches are under investigation, including aroma therapy and music therapy (Raglio et al. 2008).

Special Populations

There are several subgroups of demented patients who merit special attention and interventions. Patients with HIV-related dementia in the late stages, for example, may exhibit behavioral disinhibition, mania, and psychotic features, such as delusions and hallucinations. Primary treatment of HIV/AIDs is aimed at suppression of viral load by means of anti-retroviral therapies. Some evidence suggests that the nucleoside analog reverse transcriptase inhibitor (NRTI) zidovudine (also known as AZT) may attenuate the symptoms of HIV-related dementia and neurological impairment in some patients; however, zidovudine and related agents may themselves provoke neuropsychiatric complications, such as deper-

sonalization, mania, and delirium (Fernandez & Tan, 2008). Cognitive functioning in HIV dementia patients may be improved by methylphenidate; psychotic symptoms may respond to atypical antipsychotics, such as risperidone or olanzapine. Depression in HIV/AIDS is not uncommon, but may stem from a complex mix of direct effects of HIV on the CNS, and psychosocial factors.

Antidepressants such as citalopram and escitalopram may be useful, but this patient population is particularly susceptible to drug-related side effects and interactions. Thus, any pharmacotherapy aimed at neuropsychiatric symptoms must be very carefully monitored in this population (Fernandez & Tan, 2008).

As noted above, Dementia with Lewy Bodies (DLB) poses particular management problems. Psychotic symptoms, including visual hallucinations, are a central feature of DLB, and the sensitivity of these patients to antipsychotics makes treatment especially challenging. Cholinesterase inhibitors, such as rivastigmine, may ameliorate some neuropsychiatric symptoms in DLB patients, including hallucinations, paranoid delusions, apathy, aggression, and agitation (Simard & van Reekum, 2004; Apostolova & Cummings, 2008). If an antipsychotic must be used in DLB with psychosis, classic neuroleptics should be avoided; initiating treatment with very low doses of quetiapine or clozapine is sometimes warranted (Jacobson et al. 2007).

Depression as a feature of dementia represents a diagnostic and treatment challenge. As noted earlier, depression is commonly seen in patients with Parkinson's Disease, Huntington's Disease, DAT, and LBD, as well as in those with a history of stroke or other form of VaD. Depression may represent a prodrome to dementia or a feature of established dementia. The recently described amyloid-associated depression may represent such a prodome in DAT (Qiu et al. 2008). Vascular depression (Sneed et al. 2008; Alexopolous, 2006) may present as new-onset of depressive illness in those affected by diffuse or focal vascular lesions, and is increasingly recognized in older individuals. Conversely, the "dementia of depression" (formerly called depressive pseudodementia) is a reversible cognitive impairment directly related to the patient's mood disorder. Features such as excessive guilt, low self-esteem, self-loathing, or persistent suicidal ideation, as well as delayed responses to cognitive questions, are useful "red flags" for the presence of depression in dementia. The Cornell Scale for Depression in Dementia may be helpful in detecting this problem. Depressed patients with dementia often respond to lower doses of antidepressants (such as citalopram or sertraline) than do non-demented depressed patients (Jacobson et al. 2007).

Delirium is a common complication of both HIV-related dementia and DLB, and is discussed in the section on Delirium. Co-morbid dementia and delirium is also discussed in the section on Delirium. Case Vignette: Mr. J. was a 78-year-old nursing home patient with dementia of the Alzheimer type (DAT). The staff were concerned and distressed by Mr. J's frequent "moaning" or "yelling," particularly in the evening, and believed these behaviors were adversely affecting the other residents of the home. Mr. J. was prescribed risperidone 1.0 mg at h.s. His yelling diminished after only two days of treatment. However, he developed significant orthostatic hypotension and akathisia, and continued to "moan" nearly every night. A comprehensive medical evaluation revealed that Mr. J. suffered from severe osteoarthritis, which was worsened with attempts by the "night shift" nurses to reposition Mr. J. in his bed. A combination of acetaminophen and local heat application led to considerable relief and marked reduction in Mr. J's verbal outbursts. Risperidone was reduced to 0.25 mg at h.s., with significant improvement in Mr. J's akathisia and hypotension.

Delirium

Phenomenology (Characteristic Features of Delirium)

Delirium may be defined as an acute or subacute disturbance in cerebral functioning leading to impairment in one's level of consciousness, orientation, memory, and attention, usually characterized by "waxing and waning" over hours or days. Common accompaniments of delirium include altered sleep-wake pattern; labile mood; speech disturbance; restlessness or agitation; perceptual abnormalities; and sometimes, psychotic features. Older terms for delirium include "acute organic brain syndrome," "cerebral insufficiency," and "acute confusional state." Not uncommonly, delirium may be superimposed on dementia, a condition sometimes termed "beclouded dementia" (Sadock & Sadock, 2007).

Epidemiology

Delirium is a very common problem, particularly in emergency, medical-surgical, inpatient, and geriatric settings, such as nursing homes (Levkoff et al. 1991). Substance-abuse and oncology treatment centers also have high rates of delirium (Tasman et al. 1998). Among medical inpatients, the prevalence of delirium ranges from 11-16%, while among elderly patients admitted for acute hospital care, the prevalence ranges from 24-65%. Among elderly patients over age 65, hospitalized for a general medical condition, 10-15% will develop delirium while in the hospital. In general delirium tends to be more common among the very young and the very old, but can affect anyone at any age. Delirium is associated with longer hospital length of stay and mortality in medical surgical inpatients.

Subtypes of Delirium and Classification

Delirium is sometimes characterized according to the predominant disturbance in motor behavior; i.e., as excited ("hyperactive"), lethargic ("hypoactive") or mixed delirium (Trzepacz & Meagher, 2008). Some evidence indicates that these motor subtypes have implications for etiology, pathophysiology, presence of non-motor symptoms, and prognosis. Thus, some evidence suggests that patients with hyperactive delirium may have a better prognosis and a lower mortality rate. Hypoactive delirium may be more likely to go undetected, as one might expect from the lack of obvious agitation. However, the definition of these subtypes varies considerably among clinicians and researchers, and their reliability has been questioned. Another way of considering delirium is expressed by the terms "excitatory" and "inhibitory" syndromes, which we will discuss under Pathogenesis (Ferner, 2003).

Delirium with psychotic features—including delusional misidentification and hallucinations—may be particularly distressing to the patient, even after resolution of the delirium (Trzepacz & Meagher, 2008).

There are several ways delirium may be classified. In the ICD-10 (1993), the main categories are:

- Delirium, Not Induced By Alcohol And Other Psychoactive Substances
- Delirium, Not Superimposed On Dementia,
- Delirium, Superimposed On Dementia

- Other Delirium

In contrast, the DSM-IV categorizes delirium according to four very broad etiologies: delirium due to general medical condition; substance intoxication delirium; substance withdrawal delirium; and delirium due to multiple etiologies.

The number of general medical conditions (GMCs) causing delirium is legion. Some common GMCs include fluid and electrolyte abnormalities, hypoglycemia, infection or sepsis, head trauma, hepatic encephalopathy, viral encephalitis, renal failure, COPD and brain tumor or hemorrhage. A plethora of both prescribed and over-the-counter medications can provoke delirium, including analgesics, antibiotics, cardiac medications, anticholinergic agents, psychotropic agents, and a variety of botanicals, such as jimsonweed. (Sadock & Sadock, 2007)

Case vignette: An 84 year-old woman with a history of mild congestive heart failure, osteoarthritis, and moderate cognitive impairment thought possibly due to very early DAT appeared confused, disoriented, and hallucinating. She complained of seeing "green faces" and was initially diagnosed as "psychotic." Physical exam and routine laboratory measures were within normal limits. Her regular medication included digoxin 0.25 mg/day (digoxin level = 0.6 ng/ml; therap=0.5-2.0). Owing to her arthritic pain, she recently had been started on ibuprofen 400 mg tid. A repeat digoxin level shortly after admission showed the level to be 1.2 ng/ml (WNL). An EEG showed slowing of alpha rhythm (7-8 Hz, normal=8-12). The increase in digoxin levels was attributed to the effect of the NSAID, ibuprofen (Goldfrank, 2002). Though the absolute level of digoxin was still within the normal range, its doubling within a short period of time evidently set off the patient's confusion. Abnormal color perception—particularly in the green or yellow end of the spectrum (xanthopsia)—is a classic sign of digoxin toxicity (Piltz et al. 1993).

Assessment and Diagnostic Testing

Delirium remains a clinical diagnosis, with a careful history, physical exam, mental status exam, and review of medication and laboratory findings as the most useful diagnostic "instruments" (Sadock & Sadock, 2007). Typically, the onset of delirium is acute (over a period of hours, days, or in some cases weeks) and there is a marked change from the patient's "baseline" cognitive state. A recent change in medication; recent substance abuse/discontinuation; or some recent medical or neurological event (fall, infection, stroke, etc.) may provide the critical historical clues. The classic findings on mental status include a fluctuating level of consciousness (e.g., the patient "nods off" or drifts in and out of awareness); inability to pay attention to the examiner; disorientation to date and place (though intact orientation does not rule out delirium); impaired recent memory (e.g., inability to recall 3 of 3 items after 5 minutes); and associated features, such as disorganized thought processes (tangentiality, loose associations), perceptual abnormalities (auditory, and particularly, prominent visual or tactile, hallucinations); and psychomotor abnormalities (agitation, slowing). Affect may be quite labile, and delusions may also be present.

When delirium is superimposed upon dementia, it appears that delirium phenomenology generally overshadows that of the dementia. Thus, delirium tends to present similarly regardless of whether it is accompanied by dementia. The clinical maxim should be, "altered

mental status reflects delirium until proven otherwise," in order to prevent misattribution of delirium to the more chronic brain syndrome of dementia (Trzepacz & Meagher, 2008, p. 451). History from family members or caregivers may provide critical information suggesting a more acute change in functioning.

Physical examination may be difficult in an agitated, delirious patient, but every effort must be made to rule out head trauma, acute neurological events, and severe autonomic dysfunction (such as marked hypotension). Pulse, blood pressure, temperature, respirations should all be checked. An examination of the head and neck—including papillary function and extraocular movements—should be carried out. A basic assessment of heart, lungs, and neurological function should be obtained. Specific physical findings may provide a clue as to the etiology of the delirium. For example, a patient with papilledema and hypertension may be experiencing hypertensive encephalopathy; nuchal rigidity may point to meningitis or subarachnoid hemorrhage (Sadock & Sadock, 2007). One helpful clue may be pupillary findings: in cases of anticholinergic toxicity, pupils may be dilated but sluggish; in cases of "hyper-adrenergic" delirium (e.g., in sedative withdrawal, amphetamine/cocaine intoxication, or hyperthyroid storm), pupils may be dilated by briskly reactive (Ferner, 2003).

Adjunctive screening instruments for detecting delirium include the CAM (Confusion Assessment Method); the CTD (Cognitive Test for Delirium); and the DRS-R98 (Delirium Rating Scale, Revised 98). The CAM is probably the most widely used delirium screening test in general hospital settings, and is based on DSM-III criteria (Trzepacz & Meagher, 2008). Recently, Fanjiang & Folstein (2001) developed a simple screening scale for use by medical students, called the Three Item Delirium Scale. This requires the presence of altered consciousness plus either cognitive impairment or hallucinations; preliminary data suggest good sensitivity and specificity for delirium (Trzepacz & Meagher, 2008).

Laboratory measures and ancillary testing: There is no pathognomonic "test" for the diagnosis of delirium. However, it is important to obtain routine laboratory studies on all delirious patients, including—most urgently--complete blood count, electrolytes (including calcium, magnesium, and phosphate), renal and hepatic functions (including ammonia), serum glucose and erythrocyte sedimentation rate. Thyroid functions should also be checked. A blood and/or urine screen for drugs of abuse is helpful, and serologic tests for syphilis (such as VDRL) and HIV infection may also be indicated. An electrocardiogram (EKG) and chest radiograph are usually appropriate, in order to rule out cardiac arrhythmia, silent ischemia, or occult pneumonia among other causes. A bedside test for oxygenation is also useful. An electroencephalogram (EEG) is often advised as a standard study in the work up of delirium (Sadock & Sadock, 2007), since the EEG often reveals either generalized slowing or focal areas of hyperactivity. (Serial EEGs may also be helpful in following the "progress" of treatment, in that one may see restoration of normal (8-12 Hz) alpha rhythm as the delirium resolves). Depending upon history and specific medical presentations, ancillary tests, such as lumbar puncture, blood cultures, B12 level, and structural brain imaging (CT, MRI) may be clearly indicated. It is important to note that correction of underlying metabolic, electrolyte, or other abnormalities does not necessarily lead to immediate resolution of the delirium; typically, there is a "lag" between such corrections and the patient's level of consciousness. This is particularly true in those circumstances where CNS drug levels (e.g., lithium) may normalize more slowly than blood levels; or when correction of blood abnormalities (such as high glucose or sodium) needs to occur slowly, in order to prevent CNS complications. One should treat the patient, not the "lab slip!"

Pathogenesis of Delirium

Even though delirium may arise from a multitude of underlying causes, several unifying hypotheses have been advanced to explain the general mechanisms of most delirious states (Ferner, 2003). One such hypothesis emphasizes the balance between excitatory and inhibitory neurotransmission in the brain, and derives a broad separation of brain syndromes on this basis. For example, excitatory delirium syndromes may involve excessive augmentation of excitatory neurotransmitters, such as glutamate, dopamine and norepinephrine (serotonin may also be considered excitatory to some degree). Antagonism of certain cholinergic receptors, on this view, also constitutes an "excitatory" effect. Thus, delirium syndromes as diverse as amphetamine toxicity and poisoning with the anticholinergic agent benztropine would be predicted to have similar excitatory effects, including agitation, tachycardia, hypertension and fever. (Anticholinergic syndromes may present with the classic and memorable findings of "hot as a hare, mad as a hatter, red as a beet, dry as a bone;" i.e., fever, agitated confusion or psychosis; red skin; and dry mouth).

Inhibitory delirium syndromes, in Ferner's view (Ferner, 2003), involve agents that augment the inhibitory neurotransmitter, GABA, or act as agonists at the mu opioid receptor. Thus, in large quantities, GABA agonists such as benzodiazepines (and to some degree, ethanol) or opioids such as morphine may cause delirious states characterized by drowsiness, ataxia, respiratory suppression, and slurred speech. Pathological alterations in GABA activity--perhaps amplified by an endogenous toxin that binds to benzodiazepine receptors--have also been implicated in hepatic encephalopathy (Rummans et al. 1995). In some cases of inhibitory syndromes, "paradoxical" agitation may result from disinhibition of higher brain centers that normally suppress aggression or agitation (Ferner, 2003).

Another unifying hypothesis focuses specifically on low cholinergic and high dopaminergic transmission in delirium (Trzepacz & Meagher, 2008), as well as derangements in non-dominant, posterior parietal and prefrontal cortices. Other brain regions, including the brain stem, basal ganglia and thalamus, are likely to be involved. Importantly for the cholinergic hypothesis, a variety of disease states causing delirium are associated with cholinergic deficiency; e.g., thiamine deficiency, hypoxia, and hypoglycemia all reduce acetylcholine by affecting the oxidative metabolism of glucose and production of acetyl coenzyme-A (Trzepacz & Meagher, 2008).

The pathogenesis of delirium must also consider predisposing medical risk factors, though, as Trzepacz and Meagher note, these must not be confused with causes of delirium. Predisposing factors include but are by no means limited to: genetic risk factors (such as APOE4 genotype); old age; pre-existing cognitive impairment; use of multiple medications (especially anticholinergic agents and opioids); pre-existing cerebrovascular accident/stroke; and vitamin (especially thiamine) deficiency (Trzepacz & Meagher, 2008).

To some degree, psychological factors, as well as quality of hospital care, may also influence certain aspects of delirium. As Mohta et al. (2003) have pointed out, the experience of being in the intensive care or trauma unit may activate various psychological defense mechanisms, such as denial, regression, anger, anxiety and depression. Delirium itself may, in some cases, represent a regressive defense, though such psychodynamic hypotheses must never vitiate the clinician's search for specific physiological precipitants.

The likelihood of delirium may also be influenced by the kind of care the patient receives. For example, Inouye and coworkers (1999) evaluated 852 hospitalized older patients who were nonrandomly assigned to usual care or management with a multi-pronged intervention designed to minimize risk factors for delirium. These protocols included repeated reorientation of the patient; provision of cognitively stimulating activities; a nonpharmacologic sleep protocol; early mobilization activities and range of motion exercises; timely removal of catheters and physical restraints; use of eyeglasses and hearing aids; and early correction of dehydration. These interventions significantly reduced the incidence of delirium (15.0% in the usual care group versus 9.9% in the intervention group).

Treatment and Management of Delirium

The primary treatment of delirium entails diagnosing and correcting the underlying cause of the brain dysfunction. Thus, if an electrolyte disturbance appears to be the causal factor, one corrects it; if an infection seems to be "driving" the delirium, one treats it with appropriate anti-microbials (which may also provoke confusional states). If the patient's delirium appears due to a newly-prescribed medication, that agent is held or discontinued immediately, if clinically safe and feasible. (If one must avoid a superimposed withdrawal syndrome, the offending agent is tapered off and discontinued as rapidly as possible).

There are some "cause-specific" agents that treat a few narrowly-defined types of delirium. For example, in cases of known or suspected anticholinergic-induced delirium, the cholinesterase inhibitor, physostigmine, is indicated (and in the U.S., has FDA-approved labeling for this use). However, physostigmine is not without its own side effects, such as bradycardia. In cases of known or suspected alcohol withdrawal-related delirium (delirium tremens, "DTs"), a benzodiazepine is the treatment of choice. For benzodiazepine-induced delirium, limited data suggest that the benzodiazepine antagonist, flumazenil, may be useful (Olshaker & Flanigan, 2003).

In many cases of delirium, a specific cause is not identified, or multiple causes are suspected. If, after a thorough medical evaluation, no specific etiology is found, one is left to "manage" the neurobehavioral complications of delirium as effectively and safely as possible—and without making matters worse. Unfortunately, many psychotropic agents used to manage the behavioral complications of delirium (such as agitation or disinhibted behavior) may themselves cause confusion or exacerbation of the delirium. Thus, treatment should be as conservative as possible, avoiding high doses, or agents whose mechanisms of action overlap with those of drugs implicated in causing the delirium. For example, the hallucinogen, phencyclidine ("PCP", "Angel Dust") has complex effects on acetylcholine (Helman & Habal, 2006) that may be exacerbated if one treats PCP-induced psychosis with a highly anticholinergic phenothiazine.

For management of neurobehavioral complications of delirium (marked agitation, aggression, tearing out IV lines, etc.), the agents of choice remain the higher-potency neuroleptics, particularly haloperidol (5-40 mg/day, in divided doses) (Inouye, 2006a). Although larger doses have been used intravenously, particularly in ICU or SICU settings, these agents have risk of producing torsades des pointe arrythmias, which have been associated with lethal ventricular arrythmias, particularly in patients with hypovolemia, hypomagnesemia or other electrolyte abnormalities. (Hassaballa & Balk, 2003).

There is, however, increasing interest in use of newer "atypical" antipsychotics in this setting, and some limited data suggest they may be safe and effective (Han & Kim, 2004). Although benzodiazepines, such as lorazepam, are often administered to delirious patients, this group of agents carries significant risks in this population; e.g., paradoxical "disinhibition," worsening, or prolongation of the patient's confusion (Inouye, 2006 a,b). With the exception of delirium tremens, there are few instances of delirium in which benzodiazpines would be indicated.

There is also considerable interest in—but only preliminary evidence for—the use of cholinesterase inhibitors such as donepezil (see above, re: DAT) in delirium. Preliminary evidence has been mixed, and clinical observation suggests that any beneficial effects on confusion and memory impairment are modest and slowly-achieved (Jacobson et al. 2007). One recent controlled study (Liptzin et al. 2005) was "... unable to demonstrate a benefit for donepezil in preventing or treating delirium in a relatively young and cognitively-intact group of elderly patients undergoing elective orthopedic surgery."

Non-pharmacologic approaches to the delirious patient are an important part of good care, and include provision of "orienting cues," such as clocks and calendars; continuity of nursing care; placement of familiar objects (such as a family picture) near the patient; and therapeutic use of friends and family to create a familiar and calming environment (Rummans et al. 1995). Finally, primary prevention of delirium involves a comprehensive strategy, including: 1) recognizing and mitigating known risk factors such as dehydration, sleep deprivation, hearing impairment, etc. (Inouye et al. 1999); 2) proactive geriatric consultation, prior to planned surgery; and 3) education of staff charged with the care of high-risk patients (Trzepacz & Meagher, 2008).

Psychiatric Symptoms Secondary to General Medical Conditions

There is a complex and multidimensional relationship between psychiatric and medical illnesses. Psychiatric illness can be exacerbated by the presence of co-morbid medical illness and its management can be made more complex by pharmacologic or other management needs of medical illness. Psychiatric illness can present in general medical settings with medical symptoms secondary to psychiatric illness. Finally psychiatric disorders can be directly caused by the presence of known or occult medical/neurological illness. In this section, we will focus on this last category.

In the DSM-IV, this heterogeneous group of diagnoses comprises six main categories: psychotic disorders, mood disorders, anxiety disorders, catatonic disorders, personality alterations, and amnestic disorders. In the ICD-10, the term "organic" is applied to the first five categories; e.g., organic hallucinosis and organic delusional disorder; organic mood [affective] disorder; organic anxiety disorder; organic catatonic disorder; and organic personality disorder. We have already alluded to what we view as philosophical problems with the term "organic". For this reason, we will use the neutral designation, psychiatric symptoms secondary to general medical conditions (Psy-GMCs) as a "bridging" term to encompass both the DSM and ICD categories.

Prevalence in selected settings

The community prevalence of psychiatric symptoms secondary to general medical conditions (Psy-GMCs) is not well-established, nor is it straightforward to determine. Data from a consultation-liaison service, however, provide some sense of how common Psy-GMCs may be in certain high-risk medical settings. For example, Rundell and Wise (1989) reviewed 755 cases seen by the psychiatric C-L service in a general hospital. Fully 38% of depressed patients had some underlying medical or neurological disorder as the likely cause of their depression. The most frequent diagnoses were cerebrovascular accident; Parkinson's Disease; lupus cerebritis, HIV infection, hypothyroidism, and multiple sclerosis. With respect to manic syndromes on this C-L service, the findings were even more striking: 87% of manic patients had a diagnosis of "organic mood disorder." The most commonly-implicated causes of this "secondary mania" were corticosteroids, human immunodeficiency virus (HIV) infection, and temporolimbic epilepsy. Psychiatric clinic populations may also show a high prevalence of GMCs associated with psychiatric symptoms. Thus, Koranyi (1979) found that in a psychiatric clinic population, 18% had psychiatric symptoms that could be attributed solely to an underlying—and undetected—medical problem. On the other hand, in routine, non-general hospital, psychiatric inpatient settings, some types of Psy-GMCs may be quite rare. For example, Lo et al. (2007) found that the prevalence of "organic delusional disorder" according to DSM-III-R criteria was only 0.4% of total inpatient psychiatric admissions.

General features and phenomenology of Psy-GMCs

There are no pathognomonic signs that reliably distinguish psychiatric disturbances due to general medical ("organic") conditions (Psy-GMCs) from those due to primary psychiatric disorders. For example, with respect to manifestations of the depression itself, there are no singular objective features that would unequivocally distinguish, say, depression due to folic acid deficiency from depression seen in a typical major depressive episode. However, careful attention to (1) the onset, history, and course of the present illness; (2) the patient's age, prior medical and psychiatric illnesses, and family history; as well as (3) accompanying physical and laboratory findings, may all be of help.

For example, depressive, manic, anxious, or psychotic symptoms that appear to "track with" (correspond closely in time and intensity) the course of an underlying medical disorder may prove to be secondary to that disorder (see Case Vignette). Similarly, the onset of psychiatric symptoms following the introduction, discontinuation, or change in dosage of a particular drug should always raise the prospect of a "secondary" psychiatric syndrome.

The mental status exam may provide clues as to the "secondary" nature of the psychiatric disturbance; e.g., unusual cognitive deficits (such as severe memory impairment) in a patient presenting with anxiety (Goldman, 1992). Abnormal findings on physical examination (such as hypo- or hyperactive reflexes, signs of vitamin deficiency, etc.) and laboratory testing (such as anemia, decreased thyroid function, etc.) may also be helpful in discerning an underlying GMC.

On the other hand, correction of an underlying physical abnormality or drug toxicity does not always translate into an immediate remission of secondary psychiatric symptoms; often, there is a "lag" between correction of the underlying medical or drug-related problem and return to euthymia or baseline mental state. Indeed, as Colon and Popkin observe, sometimes—despite correction of the underlying medical problem—the secondary psychiatric

symptoms may develop "a life of their own" and persist for long periods (Colon & Popkin, 2006). Furthermore, as O'Brien et al. (2006) note,

"In some cases (e.g., adrenal insufficiency), appropriate and continued treatment of the underlying condition results in resolution of the psychiatric symptoms. In others (e.g., SLE), treatment of the underlying condition may alleviate but may also exacerbate psychiatric symptoms."

Advanced age, or older age of onset of psychiatric illness is sometimes a clue to an underlying GMC, though by no means an infallible one. Since the elderly (as well as the very young) are at greater risk for medical illnesses generally, the sudden appearance of apparent psychiatric symptoms in someone over the age of 55 ought to trigger a search for underlying medical factors (though one could say the same for a younger patient with a similarly abrupt onset of psychiatric illness). One's level of suspicion is generally highest in an older patient whose family history is "negative" for psychiatric disorders, and whose symptoms appear temporally linked to a GMC or drug-related event. In this regard, Lo et al. (2007) reported that compared to patients with (functional) Delusional Disorder, those with "Organic Delusional Disorder" usually had an older age of onset, and less frequently had a relevant family psychiatric history. Similarly, patients diagnosed with "organic mood disorder" were more likely to have a negative family history of depression, compared to medically-ill patients with a diagnosis of major depression (Yates et al. 1991). The patients with organic mood disorder were also less likely than their counterparts to have recovered fully after four years, despite similar treatment as those with major depression. As noted above, patients with older age at onset of affective illness, and without family history of depression, are more likely to have evidence of vascular CNS abnormalities on MRI than those with earlier onset illness.

With respect to temporal patterns, an important caveat is in order here: as Colon and Popkin (1996) judiciously observe:

"Many clinicians are inclined to rely heavily on a temporal relation to establish an organic etiological relation. Although temporal relation is an instructive parameter, it may be misleading and subject to errors of recall. It is also apparent that psychiatric symptoms may antedate the clinical recognition of the physical illness—that is, anxiety and depression may be the first presenting features of a medical illness." (p. 413)

Sometimes, the "phenomenology" of the syndrome may provide a clue as to its etiology, though this is far from universally the case. For example, when psychotic symptoms develop in the context of a GMC, they tend to present in a characteristic pattern. Thus, many secondary psychotic syndromes are characterized by paranoid delusions, persecutory thoughts, and ideas of reference. Delusions tend to be concrete and changeable, in contrast to the often elaborate, bizarre, and relatively stable delusions seen in, say, schizophrenia or mania. Lishman characterizes "organic delusions" as often persecutory in content, but typically "... poorly elaborated, vague, transient, and inconsistent..." (Lishman, 1998, p. 11). So, for example, the elderly patient in a nursing home who develops an "organic psychosis" may say, on Monday, "The nurses are trying to poison me." On Tuesday, the same patient may have no particular fears regarding the nurses, but may complain, "My roommate is stealing my jewelry." However, in organic delusional syndromes without clouding of consciousness, Lishman notes that "... the delusions may be more coherently organized, with a picture more closely resembling schizophrenia."

With respect to GMCs associated with anxiety, Colon and Popkin (1996) note that, "... there are few current data to indicate whether panic emerging in the medical patient differs from that seen in the primary psychiatric setting. In addition, no data are available about factors such as course and onset in the medical setting." One exception is the finding by Starkman et al. (1985) showing that in patients (N=17) with pheochromocytoma—a GMC long-associated with anxiety-- none described the severe apprehension or fear characteristic of panic attacks, and none described agoraphobia.

Depression in the medical setting is comprehensively reviewed by Rouchell et al. (1996). Again, there are no pathognomonic signs that clearly point to "secondary" or "organic depressive symptoms." In addition, the standard diagnostic criteria for major depression in DSM-IV have not been normed for individuals with co-morbid medical illness. However, Goldman (1992) offers the following clues suggesting an underlying medical cause: an atypical clinical picture; resistance to standard treatments; unexplained personality changes; and subtle cognitive findings on mental status exam.

The course of Psy-GMCs depends to a large degree on the nature of the underlying medical condition and how responsive it is to primary treatment. The course is also influenced by the extent and success of symptomatic psychiatric treatment. For example, when there is a progressive or intermittently active degenerative CNS process at work, such as multiple sclerosis, course and outcome are likely to be less favorable. On the other hand, psychiatric symptoms due to acute anticholinergic toxicity may be resolved within a matter of hours, if diagnosis and treatment proceed expeditiously.

Psychotic Disorder Due to GMC

Psychotic symptoms may result from a multitude of medical and neurological disorders, as well as from numerous drug-related side effects. Some of the more common organic etiologies are shown in Table 2.

Table 2: Medical Conditions Often Associated with Psychosis

Endocrine	Thyroid, adrenal, parathyroid, hyper/Hypo-function
Metabolic	Hypoxia, renal/hepatic failure, electrolyte abnormality, abnormal porphyrin metabolism
Infectious	Meningoencephalitis, HIV/AIDS, neurosyphilis
CNS	Tumor, Alzheimer's, Parkinson's, Huntington's, Wilson's Disease
Collagen	Lupus (SLE), temporal arteritis
Drugs	Corticosteroids, amphetamines, phencyclidine, cocaine, L-Dopa, bromocriptine, disulfiram, anticholinergics, alcohol
Oncology: Secondary Metabolic effects	Hypercalcemia in Small Cell Lung Carcinoma, Paraneoplastic syndromes

Condensed and modified from Soreff & McNeil, 1987

In the DSM-IV, Psychotic Disorder Due to GMC is sub-typed based on the predominant symptom; i.e., "with delusions" or "with hallucinations." Of course, the two often occur together. The DSM-IV also specifies that the symptoms must not occur exclusively while the patient is delirious, or be better explained by another mental disorder.

Although a plethora of medical and neurological conditions may produce psychotic symptoms, particular attention should be focused on disorders affecting the occipital and temporal regions. For example, cerebral tumors in these regions may produce hallucinations in various modalities, as well as delusions (Sadock & Sadock, 2007). The differential diagnosis of "psychosis" is therefore extremely important. In one study (Malmud, 1967) 6 of 11 patients with temporal lobe tumors initially presented with a diagnosis of schizophrenia, though other studies of patients with temporal lobe tumors have shown much lower rates of psychotic symptoms . Complex partial seizures originating in the temporal or frontal regions may also produce psychotic-like symptoms, as well as olfactory or gustatory hallucinations.

Case vignette: Ms. A, a 38-year-old white female with long history of vague medical problems, was brought to emergency room by her family because she had boarded up all the windows at her house and refused to come outside. The patient claimed her neighbors were "spying" on her and "want to do me in." She was fully oriented, and both recent and remote memory intact. There was no fluctuation in her level of consciousness. The patient denied any unusual perceptual changes, auditory, visual, or tactile hallucinations. Physical examination was essentially normal. However, laboratory studies revealed normocytic anemia, leukopenia, and red cell casts in urine. Subsequent testing for antinuclear antibody (ANA) was strongly positive; a provisional diagnosis of systemic lupus erythematosus (SLE) with cerebral involvement ("lupus cerebritis") was made.

Mood disorder due to general medical condition

The DSM-IV recognizes four main subtypes of mood disorder due to a GMC: with depressive features; with major-depressive like episode; with manic features; and with mixed features. The ICD-10 uses a slightly different scheme, differentiating organic manic disorder; organic bipolar disorder; organic depressive disorder; and organic mixed affective disorder.

As with the psychoses due to GMCs, secondary mood disorders may stem from a multitude of underlying medical and neurological conditions. In consultation-liason settings, as noted earlier, the most frequent underlying GMCs were cerebrovascular accident (including stroke); Parkinson's Disease; lupus cerebritis, HIV infection, hypothyroidism, and multiple sclerosis (Rundell & Wise, 1989). Post-stroke depression merits special attention, in that as many as 50% of all post-stroke patients experience depressive illness. A similar percentage applies to patients with pancreatic cancer, and to about 40% of patients with Parkinson's Disease (Sadock & Sadock, 2007). However, the diagnosis of depression in the medical setting is complicated by the substantial overlap between somatic symptoms related to the underlying GMC, and neurovegetative symptoms of depression (for review, see Harnett, 2001). For example, some data (Musselman et al. 1998) indicate that major depression is seen in approximately 15-20% of patients with coronary (ischemic) heart disease (IHD). However, depression may sometimes be over-diagnosed in this population if "lethargy" or "apathy" secondary to congestive heart failure is inappropriately counted as signifying major depression. There may also be over-diagnosis of depression in IHD patients who have become "demoralized"—but not clinically depressed—about their medical setbacks (Harnett, 2001).

Indeed, the pathophysiological relationship between underlying medical illness and mood disorder is quite complex. For example, it is not always clear to what degree a depressed medical patient may be "reacting psychologically" to the incapacity stemming from a GMC; or experiencing subtle but direct biochemical and immunological effects on the brain, stemming from the GMC (Harnett & Pies, in press). One illustration of this is in the area of IHD. Depression-related immune dysfunction may worsen IHD via inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor alpha). But IHD-related immune abnormalities may also contribute to depression (Kop et al. 2005). Moreover, social isolation, psychosocial stress, and low levels of perceived support are related to both depression and IHD, and could mediate bidirectional effects on these conditions (Barth et al. 2004; Lett et al. 2004). However depression is a well-established risk factor for increased mortality in post-myocardial infarction patients. In short, there are very complex relationships between underlying medical illness and the appearance of depressive symptoms.

This is also true, to some degree, with medication-related mood alterations. Establishing a causal connection between ingestion of a particular drug and the development of clinical depression is far from straightforward, notwithstanding epidemiological evidence linking some drugs with depression (Rogers and Pies, 2008). Although often mentioned as causes of drug-induced depression, beta blockers and calcium channel blockers are only weakly-linked with this side effect. In contrast, some medications—such as alpha-interferon and isotretinoin—do appear strongly, if not causally, linked with new- onset depression (Bonaccorso et al. 2002; Wysowski et al. 2001)

Case vignette: Mr. A., a 65-year-old married male without prior psychiatric history presented with a one month history of "feeling really down." He also related that, for the past three weeks or so, he had experienced vague gastrointestinal distress; decreased appetite; and a 15-lb weight loss. One month earlier, a close friend had died after a long illness, and Mr. A. attributed his sadness to this recent loss. Mental status exam was notable for a pale, cachectic individual whose affect appeared somewhat blunted, with occasional tearfulness. Cognitive examination was essentially within normal limits. Physical examination revealed an enlarged, non-tender gallbladder, and slight jaundice. Urinary amylase levels were elevated. A CT scan of the abdomen revealed cancer of the head of the pancreas with obstruction of the gallbladder.

Anxiety disorder due to general medical condition

The DSM-IV defines three main subtypes of anxiety disorder due to GMC: with generalized anxiety, with panic attacks, and with obsessive-compulsive symptoms. Although the overall prevalence of anxiety due to GMCs is not known, there is substantial evidence that medically-ill individuals have higher rates of anxiety than does the general public (Sadock & Sadock, 2007). For example, one study of patients with Parkinson's disease found that 38% of patients received a current DSM-III-R anxiety disorder diagnosis, including panic disorder, generalized anxiety disorder, and social phobia (Stein et al. 1990). Importantly, severity of anxiety was not correlated with severity of parkinsonian symptoms, cumulative duration of L-dopa exposure, or current dose of L-dopa. Similarly, among diabetic patients, the lifetime prevalence rates for phobic disorders and generalized anxiety disorders were 26.5% and 41%, respectively (Lustman et al. 1986).

As with other categories of secondary psychiatric symptoms, anxiety due to GMCs may stem from many underlying causes, as shown in Table 3. Endocrinopathies—notably,

hyperthyroidism, hypo- and hyperparathyroidism, and pheochromocytoma—are commonly associated with anxiety (as well as with depression). Cardiac arrythmias may be both the cause, and the result, of anxiety, sometimes leading to a "vicious cycle." For example, an individual with underlying heart disease who develops a "run" of supraventricular tachycardia may become very anxious upon experiencing the sensation of "palpitations", and thereby exacerbate or prolong the tachycardia. Although mitral valve prolapse is mentioned in older textbooks as a cause of anxiety (especially panic attacks), the evidence for this link is actually tenuous. One recent review (Filho et al. 2008) concluded that, "the more elaborate the study methodology, the lower the chance to observe a significant relationship between these (two) conditions."

A number of degenerative brain diseases may be associated with marked anxiety, including Alzheimer's Disease (DAT), Wilson's Disease, and Huntington's Disease. The frequency of anxiety in patients with DAT averages 48%, versus about 6% in elderly patients without DAT (Mega et al. 1996; Apostolova & Cummings, 2008).

The list of medications causing anxiety is very extensive, and includes bronchodilators, thyroid preparations, theophylline, psychostimulants (such as methylphenidate), antipsychotics, and antidepressants. A variety of over-the-counter remedies, such as antihistamines and herbal preparations, may also trigger or exacerbate anxiety. Recently, anxiety, tachycardia, and even seizures have been linked with various "energy drinks" containing high concentrations of caffeine (Clauson et al. 2008).

Table 3: Medical causes of Anxiety

Cardiopulmonary	arrhythmia, pulmonary embolism, pneumothorax
Endocrine	thyroid, parathyroid, adrenal dysfunction
Gastrointestinal	gastroesophageal reflux
CNS	meningoencephalitis, Wilson's Disease, Huntington's Disease, Parkinson's disease, complex partial seizures
Metabolic	hypoglycemia, hyperinsulinemia, hypocalcemia
Drugs/toxins || sympathomimetics, including caffeine, cocaine, amphetamines	

Modified and condensed from Colon & Popkin, 1996; and Soreff & McNeil, 1987

Case vignette: A 67 year-old. bedridden female was brought to the emergency room by her son. The patient had been experiencing severe anxiety for the past two hours. She was alert and oriented, but appeared extremely anxious and tremulous. Her breathing was rapid and patient complained of palpitations and lightheadedness. She had learned the day before that she was facing eviction from her apartment. The provisional diagnosis was "Panic attack with hyperventilation, precipitated by threat of eviction." Physical exam was notable for a pulse of 120; diaphoresis; and localized wheezes upon auscultation of the chest. A chest

radiograph was within normal limits. However, a perfusion scintiscan of the lung revealed acute pulmonary embolus, and the patient was immediately hospitalized.

Personality change due to general medical condition

DSM-IV recognizes five main subtypes of personality change due to general medical condition (PC-GMC); i.e., labile, disinhibited, aggressive, apathetic, and paranoid. However, "other" "combined" and "unspecified" subtypes allow for the almost infinite variations and combinations of personality alterations that may be observed clinically. The older term "organic personality syndrome" also subsumes these categories.

A variety of medical and neurological conditions may lead to alterations in the individual's usual personality, temperament, or life-long character traits. According to Reid (1989), the most common causes of PC-GMC ("organic personality syndrome") are head trauma, cerebrovascular accident, and space-occupying intracranial lesions. Other common causes include temporal lobe epilepsy, multiple sclerosis, chronic intoxications, endocrine disorders, and CNS infections such as neurosyphilis.

It is useful to focus on personality alterations due to lesions or dysfunction in frontal-subcortical circuits and within the temporal lobes. Tekin & Cummings (2002) have identified five parallel frontal-subcortical circuits that link specific areas of the frontal cortex to the striatum, basal ganglia and thalamus. Lesions originating in the orbitofrontal region lead to personality changes characterized by disinhibition; e.g., the patient begins to use profanity or exhibit sexually provocative behaviors. Lesions originating in the anterior cingulate portion of the frontal cortex produce an apathetic picture; e.g., a once outgoing and vociferous individual becomes withdrawn, indifferent, and uninterested in his usual activities.

Lesions or abnormal electrical activity in the temporal lobes also produce alterations in personality. For example, in temporal lobe epilepsy, the most common psychiatric abnormality is personality change (Chuang, 2006). Hyperreligiosity, hypergraphia, and hyposexuality are reportedly more common in patients with temporal lobe epilepsy than with other forms of epilepsy (Chuang, 2006), though not all neurologists accept this view. Tumors within or impinging upon the temporal lobes may also produce alterations in personality, including irritability, hypochondriasis, or an accentuation of neurotic traits. Some of these alterations may actually reflect temporal lobe epilepsy secondary to the tumor (Lishman, 1998).

Case vignette: A 63 year-old banker was fired for inappropriate sexual advances toward employee. He was subsequently picked up by the police for urinating in parking lot of exclusive restaurant and shouting obscenities. His wife described him as "just not himself over the past couple of months—it's like he has no self-control and no conscience." Neurological exam in the psychiatrist's office was essentially within normal limits, with no "focal" findings, except for abnormal grasp reflex (a tongue depressor repeatedly placed in the patient's hand led to his repeatedly grasping it). Magnetic resonance imagery (MRI) showed a large meningioma of the orbitofrontal cortex.

Catatonic Disorder Due to General Medical Condition

"Catatonia" is probably best conceptualized as a syndrome with markedly diverse etiologies. Fink and Taylor (2006) have proposed three catatonia subtypes (nonmalignant, delirious, and malignant) and four specifiers (secondary to: mood disorders, general medical conditions or toxic states, neurological disorders, or psychotic disorders).

When no identifiable medical or neurological cause is present, about 40% of cases prove secondary to mood disorders, whereas only about 10% are associated with schizophrenia (Sadock & Sadock, 2007). Catatonic disorder due to GMC is not a well-studied phenomenon, and its prevalence has not been clearly established. Features include immobility, psychomotor agitation, mutism, negativism, grimacing, peculiar motor behaviors (such as assuming and maintaining unusual postures, sometimes characterized by "waxy flexibility"), echolalia, and echopraxia. Medical and neurological causes of catatonia include drug toxicity, including neuroleptic malignant syndrome (NMS), CNS neoplasms, encephalitis, head trauma, lesions of the fronto-subcortical circuit, and contralateral parietal lobe lesions (Ovsiew, 2008). When catatonia is accompanied by fever and autonomic instability, it may represent malignant catatonia, a potentially lethal form of catatonia which needs emergent treatment with electroconvulsive therapy (ECT) (Fink & Taylor, 2006).

Case vignette: A 53-year old male presented to a psychiatrist with a provisional diagnosis of "late onset schizophrenia." The man had in fact been functioning quite well until about a year ago, when he developed insidious signs of forgetfulness, apathy, and abulia (loss of spontaneity and effort). Recently, he had also developed leg weakness and "fainting spells." However, his presentation to the psychiatrist was one of mutism and marked decrease in voluntary movements of any kind; indeed, the psychiatrist described the patient as "grossly catatonic." Given the atypical age of onset for schizophrenia, and history of leg weakness, an MRI was ordered. It revealed "ventriculomegaly; hydrocephalus secondary to subthalamic mesencephalic tumor involving the third and the lateral ventricles." Surgical placement of a ventriculoperitoneal shunt led to resolution of the catatonia over a period of several days (Neuman et al. 1996).

Amnestic Disorder due to GMC

Amnestic disorders entail impairment in the ability to learn new information, or to recall previously learned information. Amnesia is most commonly found in patients with a history of alcohol abuse or head injury, in which bilateral damage to mid-temporal lobe structures (such as the hippocampus, mamillary bodies or amgydala) has occurred. In the DSM-IV, the two primary categories are amnestic disorder due to GMC, and substance-induced persisting amnestic disorder.

Numerous GMCs may produce amnestic disorder, including thiamine deficiency, hypoglycemia, carbon monoxide poisoning, hypoxia, and herpes simplex encephalitis, all of which tend to produce bilateral hippocampal damage (Sadock & Sadock, 2007). Korsakoff's Syndrome (KS) is characterized by marked amnestic symptoms in the presence of generally preserved cognitive function in other spheres. Essentially, KS is the chronic amnestic phase of Wernicke-Korsakoff Syndrome. Though the predominant defect in KS is usually anterograde amnesia—i.e., impaired ability to retain new memories--there is often a retrograde amnestic component as well. Usually, there is relative sparing of remote memory. Lishman (1998) has noted that the line between Korsakoff's Syndrome and so-called alcoholic dementia is not always sharp, and there are most likely gradations or intermediate states between these two conditions. KS–though conventionally attributed to thiamine deficiency—is closely associated with alcohol abuse and dependence. Indeed, Lishman (1998) goes so far as to opine that, "...the rarity of a fully fledged Korsakoff syndrome as a residue of thiamine deficiency in non-alcoholics raises the possibility that a direct neurotoxic action of alcohol may play some part in the evolution of the condition (p. 582)."

Medical and Laboratory Evaluation for Psy-GMC

Given the prevalence of undetected medical illness in psychiatric populations, it is incumbent upon the physician to treat all putative "psychiatric" symptoms with a certain degree of skepticism. As noted earlier in this chapter, one's degree of suspicion is raised when the patient presents with a recent change in mental status, particularly when this occurs in temporal proximity to a known medical illness or drug-related event. Atypical presentations; late-life onset; and illness that fail to respond to standard therapies should all raise ones suspicion of a medical cause. The basic "work up" of suspected psychiatric symptoms due to GMC is outlined in Table 4.

Table 4: Physical Evaluation, Laboratory and Other Investigations for Psy-GMC

Physical evaluation	Vital signs; assess for pain complaints; gross physical exam immediately; complete physical ASAP with close attention to neurologic exam and detailed mental status examination
Laboratory investigations	Complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, VDRL (screening for syphilis), liver function tests, thyroid function tests, serum calcium, magnesium, phosphate, ammonia, erythrocyte sedimentation rate, HIV testing (where risk factors are present)
Other investigations	Electrocardiogram, chest radiograph in selected cases, O2 saturation, urinalysis/drug screen, ? EEG (helpful in confirming, monitoring delirium)

Treatment of Psy-GMCs

Treatment of individual Psy-GMCs is beyond the scope of this chapter, since it necessarily focuses on primary treatment of the numerous underlying medical conditions. Symptomatic treatment with psychotropic agents may be conservative for Psy-GMCs, and depends on whether the predominant disturbance is in the realm of mood, reality testing (psychosis), anxiety, personality, etc. Though psychotropics aimed at a particular GMC-related symptom may sometimes be useful—e.g., antipsychotics for "organic" psychosis, or antidepressants for depression due to a GMC—most psychotropics run the risk of further clouding the patient's mental state, or introducing side effects and drug-drug interactions. Nevertheless, there is a role for judicious use of psychotropics in certain instances; e.g., antidepressants in post-stroke depression, or depression related to Parkinson's disease.

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16 Psychopharmacology

The use of psychotropic medicines to treat psychiatric illness has increased dramatically in recent times. Although the biological etiologies of most psychiatric disorders are still unclear, effective pharmacological treatments have been developed over the past 50 years that have become part of the standard of care in the treatment of most major psychiatric disorders.

Psychiatric medications are part of the armamentarium of most practicing physicians, regardless of medical specialty. In the United States, although most severe types of mental illness are likely to be treated by psychiatrists, most prescriptions for psychotropics (e.g., anxiolytics and newer antidepressants) are written by non-psychiatrists.(Stagnitti, 2008) Psychiatric medications are consistently prominent in the list of the top 200 most commonly prescribed medications, and in the top 20 pharmaceuticals in terms of sales in the United States. From 2003-2007 antidepressants, as a class, topped all other therapeutic classes for the overall number of dispensed prescriptions in the U.S.(IMS Health, 2007)

As in the treatment of all medical disorders, a thorough evaluation must precede psychiatric diagnosis and subsequent psychopharmacological treatment. A complete history should be obtained and the patient should be examined. Medical or neurological etiologies that may contribute to the presentation of psychiatric illness should be identified and addressed. Nearly 10% of patients presenting with a psychiatric complaint will turn out to have a medical problem as the primary cause.(Hall, Popkin et al. 1978) Active substance abuse, if present, should be treated before or at the same time that pharmacological therapies are initiated.

The clinician should then decide if the condition requires medication treatment. Mild to moderate anxiety and depression generally respond equally well to supportive interventions or psychotherapy.(APA, 2004; Barkham and Hardy, 2001; Cuijpers, van Straten et al. 2009; King, Sibbald et al. 2000) On the other hand, if the psychiatric disorder or symptoms are severe, or if psychosis, mania, or dangerousness are present, then psychopharmacological treatments (and referral to a psychiatrist) are indicated. Although many primary care physicians may be quite comfortable with their ability to manage psychiatric illness, the amount of monitoring that is required to provide adequate follow-up should be taken into account before initiating treatment. When treating moderate to severe psychiatric illness, optimum therapy includes the use of concomitant psychotherapy in addition to pharmacotherapeutic measures.(APA, 2004; APA, 1998; APA, 2000; Keller, McCullough et al. 2000; Banerjee, Shamash et al. 1996; Reynolds, Frank et al. 1999; Katon, Von Korff et al. 1999; Miklowitz, 2008)

Placebo-controlled randomized clinical trials, using strict exclusionary criteria when selecting subjects, have traditionally been used to study a psychiatric medication's efficacy (i.e., the ability of the medication to treat the condition better than placebo under controlled conditions). For example, studies comparing an antidepressant to placebo may use an 8 week double-blind parallel design and include subjects with major depression but without any

other medical or psychiatric co-morbidities. Response may be defined as a 50% improvement in a chosen outcome rating scale. These efficacy studies also provide the response data that pharmaceutical companies must submit to the Food and Drug Administration (FDA) to obtain indications for developed drugs.

Effectiveness studies, on the other hand, are often larger, naturalistic studies that attempt to approximate "real world" conditions by studying patients who may have psychiatric and medical co-morbidities, and by relying on broader outcome measures for assessing response. These studies may compare outcomes of treatment with multiple medications. As such, effectiveness studies complement our understanding of drug efficacy.(Summerfelt and Meltzer, 1998) Recent National Institute of Mental Health (NIMH) sponsored effectiveness studies have the added benefit of funding from a neutral (non-pharmaceutical industry) source, thereby avoiding possible study design shortcomings or evaluator biases that may influence study results.(Heres, Davis et al. 2006; Osser, 2008) These studies include (1) the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),(Keefe, Bilder et al. 2007; Lieberman, Stroup et al. 2005) (2) the Sequenced Treatment Alternatives to Relieve Depression Study (STAR*D),(Rush, Trivedi et al. 2006; McGrath, Stewart et al. 2006; Nierenberg, Fava et al. 2006; Trivedi, Fava et al. 2006; Fava, Rush et al. 2006) (3) the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),(Sachs, Nierenberg et al. 2007; Goldberg, Perlis et al. 2007; Miklowitz, Otto et al. 2007) (4) the Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD),(Schneider, Tariot et al. 2006; Sultzer, Davis et al. 2008) and (5) the National Institute of Alcohol Abuse and Alcoholism (NIAAA) sponsored Combined Pharmacotherapies and Behavioral Interventions Study (COMBINE).(Anton, O'Malley et al. 2006; Anton, Oroszi et al. 2008) Findings from these studies are now influencing clinical psychiatric practice.

In clinical practice, even after an appropriate diagnosis is made for an individual patient and the decision is made to use a medication from a particular pharmacotherapeutic class (e.g., an antidepressant for depression), multiple variables need to be considered prior to selecting a specific agent. The physician should take the following into account: (1) patient acuity and the need to address the most dangerous presenting symptoms (e.g., behavioral agitation, suicidality, catatonia, etc.) first, (2) the patient's past treatment history, (3) pre-existing medical conditions in order to minimize any increase in medical risk, (4) possible medication interactions, (5) the time required for amelioration of symptoms, (6) a medication's known side effect profile and how this may affect presenting symptoms, (7) the need to minimize the use of polytherapy, (8) possible pharmacogenetic factors and hereditary patterns of drug response and tolerance, and (9) financial cost-benefit considerations. The practicing physician should consider these issues prior to initiating treatment.(Ansari, Osser et al. 2009)

Characteristics of the major classes of psychotropics and their use in adults are discussed below. Children and adolescents may tolerate or respond to these medications differently. The use of psychopharmacological therapies in these age groups is outside the scope of this chapter.

16.1 Antidepressants

Currently available antidepressants primarily affect the norepinephrine and serotonin (monoamine) neurotransmitter systems.(Nestler, Hyman et al. 2009) Norepinephrine systems originate primarily from the locus ceruleus (and lateral tegmental areas) and project widely to almost all areas of the brain and spinal cord. Serotonergic neurons reside in the raphe nuclei in the brainstem and diffusely make contact with all areas of the brain. Most antidepressants increase the available amount of norepinephrine and/or serotonin at the neuronal synapse by decreasing the reuptake of these neurotransmitters into the pre-synaptic cell. They do this by inhibiting the norepinephrine transporter and/or the serotonin transporter, or by decreasing the metabolism of these neurotransmitters. Other antidepressants have direct effects on monoamine receptors. Genetic polymorphisms of the norepinephrine and serotonin reuptake transporters (Kim, Lim et al. 2006) as well as polymorphisms of post-synaptic serotonin receptors(McMahon, Buervenich et al. 2006) have been associated with differences in responses to different antidepressants. Once synaptic changes have taken place with treatment, long-term adaptations in post-synaptic neurons and resultant changes in gene expression may then be responsible for alleviating depression.(Nestler, Hyman et al. 2009)

16.1.1 Tricyclic Antidepressants (TCAs)

Beginning with the introduction of imipramine in the late 1950's,(Kuhn, 1958) tricyclic antidepressants were among the first classes of antidepressants developed. They share a tricyclic structure (two benzene rings on either side of a seven-member ring), exhibit variable degrees of norepinephrine and serotonin reuptake inhibition, and are antagonists at several other neurotransmitter receptors.(Hyman, Arana et al. 1995) Examples of commonly used TCAs include the tertiary amines imipramine, amitriptyline, clomipramine, and doxepin, and the secondary amines desipramine (metabolite of imipramine) and nortriptyline (metabolite of amitriptyline). All TCAs can cause the following adverse effects: (1) slowing of intra-cardiac conduction as measured by QRS and QTc prolongation, (2) anticholinergic effects such as dry mouth, urinary retention, and constipation due to muscarinic acetylcholine receptor antagonism, (3) orthostatic hypotension due to peripheral alpha-1-adrenergic antagonism, and (4) sedation and possible weight gain due to histamine (H1) receptor antagonism. For these reasons TCAs need to be started at low doses and increased gradually, giving the patient time to accommodate to these effects. Individual differences in both severity of side effects and therapeutic effects (along with differences in therapeutic serum levels)(Perry, Zeilmann et al. 1994) do exist among individual TCAs. There is some evidence to suggest that TCAs may have a particularly important role in the treatment of severe and psychotic depression.(Hamoda and Osser, 2008)

The cardiac effects of TCAs have contributed to a reduction in their use over the past 20 years. Prolonged QT interval (measured as QTc when corrected for heart rate) may be associated with torsades de pointes, a potentially fatal ventricular arrhythmia (also see section on antipsychotics). All patients should have an ECG to rule out any existing conduction abnormalities prior to considering TCAs. Patients with recent myocardial infarctions should not initiate treatment with these antidepressants. Most importantly, depressed patients who are at risk for suicide and overdose may not be appropriate for treatment with TCAs. It should be noted that a 1-2 week supply of these medications can be fatal in overdose due

to the risk of cardiac arrhythmias. Therefore, depending on the patient's risk of suicide, clinicians may need to limit the number of tablets prescribed with each refill. This concern is significantly lessened with the use of newer antidepressants that are safer in overdose.

TCAs are often used for their mild to moderate analgesic effects in the treatment of chronic pain syndromes.(Magni, 1991) These effects are independent of any effect on mood, with efficacy starting at lower doses, and with response seen earlier than when antidepressants are used for depression.(Magni, 1991; Max, Culnane et al. 1987; Onghena and Van Houdenhove, 1992) The TCAs seem more effective for chronic pain than the selective serotonin reuptake inhibitor antidepressants (SSRIs, see below).(Ansari, 2000; Fishbain, 2000; Saarto and Wiffen, 2007)

16.1.2 Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase is an enzyme that acts to metabolize monoamines, both intracellularly and extracellularly. Its inhibition increases the amount of serotonin, norepinephrine and dopamine available for neurotransmission. The first MAOI, iproniazide, an anti-tuberculosis drug, was discovered in the 1950's. Tranylcypromine, phenelzine, isocarboxazid, and more recently transdermal selegiline are MAOIs currently available in the United States for the treatment of depression. These antidepressants may be particularly effective for patients with atypical depression (i.e., depression characterized by hyperphagia and hypersomnia).(Quitkin, Stewart et al. 1993)

Although serotonergic side effects—see SSRIs below—as well as orthostatic hypotension can occur with MAOIs, there are two other primary areas of concern that limit the use of these agents.(Lippman and Nash, 1990) First, dangerous interactions can occur with certain foods, such as aged cheeses and wines that contain biogenic amines such as tyramine. MAOIs can inhibit the metabolism of tyramine in the intestine, increasing its general circulation and ultimately leading to an increase in sympathetic outflow and an adrenergic ("hypertensive") crisis characterized by severe hypertension, headache, and increased risk of stroke and cerebral hemorrhage. Patients need to be advised regarding dietary restrictions before treatment. Also, to prevent hypertensive crisis, MAOIs cannot be combined with medications that have sympathomimetic properties such as some over the counter cold preparations, amphetamines, and epinephrine (which is often added to local anesthetics as a vasoconstrictor).

Secondly, MAOIs if used concomitantly with serotonergic agents, such as SSRIs, may lead to "serotonin syndrome," a potentially fatal condition that is characterized by hyperreflexia, hyperthermia, and tachycardia, and may lead to delirium, seizures, coma and death.(Sternbach, 1991) A two week washout period is required when switching from SSRIs (or any other agents with serotonergic effects) to MAOIs, or vice versa. An exception is when the long half-life SSRI fluoxetine is being discontinued: a five week washout period is needed before starting an MAOI.(Boyer and Shannon, 2005) The treating physician should access appropriate online databases such as the drug-specific DRUG-REAX® System (www.micromedex.com/products/drugreax) or GeneMedRx (www.genemedrx.com) to rule out dangerous drug-drug interactions when considering the use of an MAOI.

16.1.3 Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are antidepressants with a more favorable side effect profile than TCAs and MAOIs and as such are used as first-line antidepressants. As their name implies, SSRIs inhibit the serotonin transporter from reuptaking serotonin at the neuronal synapse. Interestingly, polymorphisms at the promoter region of the serotonin transporter gene (SLC6A4) may influence response to SSRIs: the presence of the "short" form of the serotonin transporter gene may be associated with poor response to SSRIs, whereas the presence of the "long" allele may be associated with positive drug response (Malhotra, Murphy et al. 2004) and better tolerability.(Murphy, Hollander et al. 2004) Recent data from the large NIMH STAR*D study, however, have failed to support the association between this polymorphism and drug response.(Kraft, Peters et al. 2007; Lekman, Paddock et al. 2008)

Currently available SSRIs include fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram and its S-enantiomer escitalopram. Possible mild early side effects (that can be minimized by starting the SSRI at a low dose and increasing the dose gradually) include gastro-intestinal upset, sweating, headaches, jitteriness or sedation. Continuation of these agents may be associated with reversible sexual side effects (i.e., delayed ejaculation, decreased libido, or erectile dysfunction) in 2-73% of treated patients (depending on how questions regarding sexual side effects are asked).(Montejo, Llorca et al. 2001)

SSRIs differ in their propensities to inhibit hepatic cytochrome P450 enzymes (e.g., CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4).(Ereshefsky, Jhee et al. 2005) Inhibition of hepatic enzymes may lead to decreased metabolism of substrate medications such as warfarin, metoprolol, tricyclic antidepressants, and antipsychotics. This may increase serum levels of these drugs and lead to increased risk of dangerous adverse effects such as bleeding, hypotension, cardiac arrhythmias, and parkinsonian effects, respectively. Among the SSRIs, citalopram and escitalopram are the least likely to inhibit the metabolism of other drugs and are therefore preferred in patients concomitantly treated with multiple other medications. Escitalopram is a more recently marketed, and still expensive, successor to generic citalopram, though it has no clinically significant efficacy advantage.

The relatively benign side effect profiles of SSRIs and their ease of use have contributed to widespread use by clinicians who might not have been comfortable with using earlier antidepressants such as TCAs and MAOIs. In cases of atypical presentations of depression, or depression in the context of recent substance abuse, SSRIs are more readily used even before there is absolute clarity in diagnosis. Under these circumstances, many clinicians believe that the benefits of treatment may outweigh the risks. In the case of depressed patients with concomitant substance abuse, the possibility that some patients may not be able to maintain sobriety because of an underlying major depressive disorder has served as a rationale for beginning antidepressant therapy even when the patient is still actively using.

Although this empirical "trial" of an SSRI (as an antidepressant with a relatively benign side effect profile), in situations where there is less than optimum diagnostic clarity, may be appropriate for some patients, the physician should be aware of at least two major areas of risk. First, all antidepressants can induce mania in the short-term, and overall mood instability in the long-term, in patients with a vulnerability to bipolar disorder. A clear family history should be obtained to investigate whether there is a genetic predisposition to bipolar disorder. Also, clinicians should be aware that younger depressed patients, who may go on

later to exhibit manic symptoms, may be incorrectly diagnosed with unipolar depression when in fact they may have a bipolar diathesis. A pre-bipolar presentation of depression (O'Donovan, Garnham et al. 2008) should be suspected in patients with (1) a family history of bipolar depression, (2) a younger age of onset, (3) a family history of completed suicide, (4) past poor response to antidepressants, (5) a history of treatment-emergent agitation, irritability, or suicidality, and (6) a history of post-partum psychosis.(Chaudron and Pies 2003) Depressed patients with these characteristics may have bipolar rather than unipolar depression and therefore should not be reflexively started on an antidepressant.(Ghaemi, Ko et al. 2002; O'Donovan, Garnham et al. 2008; Phelps, 2008)

Secondly, antidepressants have been associated with an increased risk of treatment-emergent suicidality—this occurs in about 4% of treated patients versus 2% on placebo—especially in children, adolescents and young adults as noted in the current package inserts of all antidepressants. It is still unclear if this risk is significant in adults over age 25. The reasons for this increase in suicidality are not clear, although increased agitation (e.g., akathisia) or activation as a side effect,(Harada, Sakamoto et al. 2008) or the possible emergence of "mixed" manic symptoms (mania combined with dysphoric mood) in depressed bipolar patients as noted above, may be responsible. Despite the concern that antidepressants may infrequently increase suicide risk, it should be noted that overall rates of suicide in the United States had actually decreased over a prior 15 year span probably due to the increasingly widespread use of SSRI antidepressants.(Grunebaum, Ellis et al. 2004) Nevertheless, the concern about treatment-emergent suicidality argues for the need for careful evaluation and diagnosis, increased discussion of risks and benefits of treatment with patients (and family when appropriate), and close monitoring of all patients beginning antidepressant therapy. Prescribing antidepressants when indicated, coupled with these steps, is more appropriate than withholding antidepressants in unipolar depressed patients who are more likely to benefit rather than come to harm from these treatments.(Bridge, Iyengar et al. 2007) Unfortunately, recent surveys have found that instead of the increase that was hoped for in the monitoring of patients undergoing antidepressant therapy,(Morrato, Libby et al. 2008) there has been an overall decrease in the use of antidepressants and a recent increase in the overall rates of suicide(Gibbons, Brown et al. 2007) since the "black box" warnings about treatment-emergent suicidality were issued.

16.1.4 Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

The SNRIs, venlafaxine, desvenlafaxine and duloxetine, are dual action serotonergic and noradrenergic antidepressants that would be expected to have efficacy similar to TCAs though without anticholinergic, antihistaminic, hypotensive, or cardiac side effects. Venlafaxine is primarily serotonergic at lower doses and has a dual action only at higher doses.(Feighner 1999; Richelson 2003) Using venlafaxine at lower doses (i.e., less than 150 mg per day), therefore, should not be presumed to be any different from using an SSRI. At higher doses it can have a mild to moderate hypertensive effect,(Johnson, Whyte et al. 2006; Mbaya, Alam et al. 2007) although patients with effectively treated hypertension can tolerate venlafaxine without an increase in blood pressure(Feighner, 1995). Duloxetine, which exerts a dual action effect throughout its dose range (i.e., not only at higher doses as with venlafaxine),(Stahl and Grady, 2003) can also increase blood pressure, although the effect may be less pronounced and clinically insignificant.(Raskin, Goldstein et al. 2003; Wohlreich, Mallinckrodt et al. 2007)

SNRIs, like TCAs, are more likely to induce mania in bipolar patients than SSRIs.(Leverich, Altshuler et al. 2006)

Because low-dose TCAs have been shown to be modestly effective in the treatment of chronic pain syndromes, and SNRIs have a similar dual action, they have been proposed for the treatment of chronic pain symptoms as well. Duloxetine is currently the only antidepressant with an FDA indication for diabetic neuropathy and fibromyalgia. Although the more benign side effect profile of duloxetine may make it the preferred agent in a patient for whom the risks associated with a TCA are unacceptable, there is no evidence to suggest it would be more efficacious for the treatment of pain than the more cost-effective TCAs.

16.1.5 Antidepressants with Other Mechanisms

Bupropion is an antidepressant with a poorly understood mechanism of action. It is believed to exert its effect through dopamine reuptake inhibition although it is unclear why this mechanism alone should provide it with an antidepressant effect. Some data suggest that it may also exhibit norepinephrine reuptake inhibition.(Richelson, 2003; Rosenbaum, Arana et al. 2005) Bupropion has a different side effect profile than antidepressants that significantly affect the serotonergic systems. It is unlikely to cause sexual side effects or weight gain—two of the most common reasons for medication non-adherence in patients. However, bupropion can lower seizure threshold and is therefore contraindicated in patients who are seizure-prone (e.g., patients with a history of seizures or conditions that increase seizure risk, such as eating disorders, or active withdrawal from alcohol or benzodiazepines). The risk of seizure is dose dependent: this should be kept in mind when combining bupropion with CYP2D6 inhibitors such as paroxetine or fluoxetine that may increase bupropion serum levels. Among antidepressants, bupropion is least likely to cause mania in bipolar patients.(Leverich, Altshuler et al. 2006; Post, Altshuler et al. 2006)

Mirtazapine increases both serotonin and norepinephrine at the neuronal synapse (and therefore like SNRIs has "dual actions") through mechanisms distinct from reuptake inhibition. It is an antagonist at alpha-2-adrenergic autoreceptors thereby increasing norepinephrine and serotonin release, and it blocks post-synaptic 5HT-2A, 5HT-2C, and 5HT-3 serotonin receptors.(Feighner, 1999) (Mianserin, an earlier analog of mirtazapine marketed in Europe, has a similar mechanism of action). Mirtazapine can improve appetite (likely through 5HT-3 and H1 antagonism) and sleep (through H1 antagonism). As expected, these immediate effects can be very beneficial in the treatment of the acutely depressed patient with poor oral intake and insomnia. Weight gain however can be a concern over the long run.

Nefazodone is a post-synaptic 5HT2 antagonist with weak serotonin and norepinephrine reuptake inhibition.(DeVane, Grothe et al. 2002) Although nefazodone can improve sleep, and is neutral in regard to weight gain and less likely than SSRIs to cause sexual side effects, it is used much less often since it was found to produce rare (1 in 250,000 to 300,000 patient-years), but severe, hepatotoxicity.(Gelenberg, 2002) Trazodone, a structurally similar antidepressant, is used primarily as a hypnotic (it proved to be too sedating for most patients at doses necessary for antidepressant effect). Trazodone can commonly cause orthostasis and should be used cautiously in the elderly. Priapism is a rare side effect that should be discussed with male patients before treatment.

16.1.6 Further Notes on the Clinical Use of Antidepressants

Clinical practice today emphasizes the use of newer ("second generation") antidepressants including bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone and venlafaxine. As discussed above, the older tricyclics and MAOIs are not first-line because of their greater toxicity and risk of harm from overdose. In a meta-analysis of 203 studies comparing the efficacy and side effects of these newer antidepressants, no substantial differences in effectiveness were found.(Gartlehner, Gaynes et al. 2008) The authors recommended that antidepressants be selected on the basis of differences in expected side effects and cost (i.e., – use generic products over brand items). Another review of 117 trials concluded that sertraline had the most favorable balance among benefits, side effects, and acquisition cost.(Cipriani, Furukawa et al. 2009)

The STAR*D study (Sequenced Treatment Alternatives to Relieve Depression), sponsored by the NIMH was a study of medications for the treatment of major depression. It produced important insights into the optimum use of pharmacotherapy for this disorder. STAR*D started with almost 4,000 heterogeneous "real world" depressed patients, who were treated by "real world" clinicians such as primary care doctors. Patients agreed to have up to 4 medication trials with the goal of achieving remission from their depression. Each trial lasted up to 14 weeks. Patients started with citalopram for the first trial. If response was unsatisfactory, they could have a switch to one of three antidepressants, or an augmentation with one of two augmenting agents. For the third trial, there were other switches or augmentations available, and finally for those still depressed and still willing to undergo the fourth trial, there was the choice of an MAOI or a combination of venlafaxine and mirtazapine. The latter has been referred to informally as "rocket fuel" because of the four different neurotransmitter alterations that this combination is thought to induce.(McGrath, Stewart et al. 2006) Key findings from STAR*D include the following:

- Citalopram did not work well if patients met the DSM-IV criteria for melancholic features.(McGrath, Khan et al. 2008)
- The switches in the second trial (to another SSRI: sertraline, to bupropion, or to venlafaxine) had equal efficacy.
- The augmentations in the second trial (buspirone--discussed in anxiolytic section below--or bupropion) worked equally well.
- Nothing worked well in trials one or two if patients had significant anxiety symptoms along with their depression.(Fava, Rush et al. 2008) However, a recent study with adjunctive aripiprazole (an antipsychotic discussed below) added to an SSRI found good results in patients with depression mixed with anxiety, in a post-hoc analysis.(Trivedi, Thase et al. 2008) This needs replication in a prospectively designed study.
- In the third trial, switching to a tricyclic antidepressant worked fairly well. It might have worked better if clinicians had dosed it properly and used plasma levels to monitor adequacy of dosage.
- Adding lithium (discussed in the mood stabilizer section below) did not work as well as adding triiodothyronine in the third trial, but lithium might have done better if clinicians had dosed it properly.

- In trial 4, the MAOI did not do well compared to the venlafaxine/mirtazapine combination, but clinicians underdosed the MAOI. Unfortunately, for the few patients who improved from either treatment, early relapse was common.

As a group, STAR*D subjects were not particularly interested in psychotherapeutic treatment for their depression. Psychotherapy was available as an option in the second treatment trial, but patients could elect to drop it from the option list and most did so.(Wisniewski, Fava et al. 2007) The modest remission rates seen in STAR*D may reflect that a major component of the improvement in depression seen in research and clinical settings comes from the non-specific, interpersonal supportive aspects of care including the therapeutic alliance. STAR*D patients might have been less susceptible to these benefits than other patients who are more invested in psychosocial treatments of their disorder. It is hoped that future studies will improve our ability to select the best treatments for each patient, psychopharmacological and psychotherapeutic, depending on their needs and preferences.

Table 1 summarizes characteristics of commonly used antidepressants.(WHO, 2007; PDR, 2008; Hyman, Arana et al. 1995; Perry, Zeilmann et al. 1994; Rosenbaum, Arana et al. 2005; Stahl 2005; Taylor, Paton et al. 2007)

TABLE 1. COMMONLY USED ANTIDEPRESSANTS

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Imipramine (TCA)(Tofranil®)	See nortriptyline, except increase gradually to 100-200 mg po qhs	Check baseline ECG; therapeutic serum level of imipramine + its metabolite desipramine: 175-350 ng/mL; TCA most commonly used in comparative anxiety studies; CYP1A2, CYP2D6 substrate.Depression/Temporary adjunct in childhood enuresis in patients greater or equal to 6 years of age

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Amitriptyline (TCA)(Elavil®)	See nortriptyline, except increase gradually to 100-200 mg po qhs	Check baseline ECG; possible therapeutic serum level of amitriptyline + its metabolite nortriptyline: 93-140 ng/mL; frequently used in low doses for chronic pain; most anticholinergic TCA; TCA with most overall adverse effects; CYP1A2, CYP2D6 substrate. On WHO Essential Medicines List for depressive disorders.Depression
Clomipramine (TCA)(Anafranil®)	See nortriptyline, except increase gradually to 100-200 mg po qhs	Check baseline ECG; most serotonergic TCA; CYP1A2, CYP2D6 substrate. On WHO Essential Medicines List for OCD and panic attacks.OCD
Doxepin (TCA)(Sinequan®, Adapine®)	See nortriptyline, except increase gradually to 100-200 mg po qhs	Check baseline ECG; very sedating TCA, usually used as adjunct for insomnia; CYP2D6 substrate.Depression/Anxiety
Desipramine (TCA)(Norpramin®)	See nortriptyline, except give in am and/or in divided doses, gradually increase to 100-200 mg/-day	Check baseline ECG; serum therapeutic level of desipramine: greater than 115 ng/mL; least sedating (possibly activating) TCA; most noradrenergic TCA; CYP2D6 substrate.Depression
Nortriptyline (TCA)(Aventyl®, Pamelor®)	Start: 10-25 mg po qhs and increase by 10-25 mg every 2 days until 50-150 mg/day in divided doses then check serum level	Check baseline ECG; therapeutic serum level of nortriptyline: 58-148 ng/mL (TCA with most defined serum level—inverted U dose-response curve); TCA with least postural hypotension so best for use in elderly; CYP2D6 substrate.Depression

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Phenelzine (MAOI)(Nardil®)	Start: 15 mg po bid and increase weekly by 15 mg/day to 45-60 mg/ day	Nonselective MAOI; dangerous medication and food interactions (see package insert).Atypical and other depressions not responsive to other antidepressants
Tranylcypromine (MAOI)(Parnate®)	Start: 10 mg po bid and increase weekly by 10 mg/day to 30-60 mg/day	Nonselective MAOI; dangerous food and drug interactions (see package insert).MDD without melancholia
Transdermal Selegiline (MAOI)(Emsam®)	Start: 6 mg transdermal q day then increase by 3 mg patches as needed to max of 12 mg/day	Selective MAO-B inhibitor;at 6 mg dose may not need diet restrictions (but perhaps with less antidepressant effect), but at higher doses a nonselective MAOI and needs diet restrictions; dangerous food and drug interactions (see package insert).MDD
Fluoxetine (SSRI)(Prozac®, Prozac Weekly®, Sarafem®)	For fluoxetine, Prozac:Start: 5-20 mg po q am then hold at 20 mg for 4 weeks then increase by 20 mg every 4 weeks as tolerated, stop if no improvement after 4 weeks at 60 mg/day	SSRI with longest $\frac{1}{2}$ life, metabolite norfluoxetine with even longer $\frac{1}{2}$ life; works a little slower than other antidepressants; inhibits CYP2C9, CYP2D6, CYP3A4. On WHO Essential Medicines List for depressive disorders.MDD/OCD/PMDD/Bulimia/Panic Disorder

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Paroxetine (SSRI)(Paxil®, Paxil CR®)	For paroxetine, Paxil:Start: 10-20 mg po qhs and increase in 2-4 weeks to 30-40 mg/day as tolerated	SSRI most likely to cause discontinuation symptoms; SSRI most associated with treatment-emergent suicidality; only SSRI that produces weight gain; may have most sexual side effects;inhibits CYP2D6. MDD/OCD/-Panic Disorder/ Social anxiety disorder PTSD/-GAD/PMDD
Sertraline (SSRI)(Zoloft®)	Start: 25-50 mg po q day and maintain for 2-4 weeks, increase by 50 mg/day every 4 weeks if needed, maximum 200 mg/day but unclear if more helpful than 100 mg/day	Less enzymatic inhibition than fluoxetine, paroxetine, and fluvoxamine (although may increase lamotrigine levels); well-tolerated SSRI; may have the most favorable balance among benefits, side effects, and cost.MDD/PMDD/Panic disorderPTSD/Social anxiety disorder/OCD
Fluvoxamine (SSRI)(Luvox®, Luvox CR®)	For fluvoxamine, Luvox:Start: 25 mg po bid and increase in 4 days to 100 mg/day in single or divided doses, may increase to 200 mg/day in divided dose if needed	Primarily used for OCD in U.S. due to initial application to FDA for this indication; inhibits CYP1A2, CYP2C9, CYP2C19, CYP3A4.OCDSocial anxiety disorder
Citalopram (SSRI)(Celexa®)	Start: 10-20 mg po q day and increase to 40 mg/-day in 7 days, (20 mg/-day may equal placebo in some studies), increase to 60 mg/day if necessary but unclear if more helpful	Least likely SSRI (along with escitalopram) to cause medication interactions; well tolerated overall.Depression

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Escitalopram (SSRI)(Lexapro®)	Start: 10 mg po q day, increase to 20 mg/day in 2 weeks if necessary	S-citalopram; well tolerated; low risk of medication interactions; a non-generic SSRI therefore expensive; comparison with citalopram showed about 15% better efficacy with escitalopram but this may have been an artifact of doses used.MDD/GAD
Venlafaxine (SNRI)(Effexor®, Effexor XR®)	For venlafaxine, Effexor:Start: 37.5 mg po q day for 4 days then increase to 75 mg daily, then add 75mg/day every week until 225 mg/day	Check baseline blood pressure, then every 3-6 months; an SSRI at low doses; >150 mg needed for norepinephrine effect—but increases blood pressure at these higher doses; high risk of discontinuation syndrome; low risk of enzyme inhibition; venlafaxine is the only generic and inexpensive SNRI.Depression/GAD/Social anxiety disorder/Panic disorder
Duloxetine (SNRI)(Cymbalta®)	Start: 40 mg/day in single or divided doses, increase to 60 mg/day in divided doses after 3-7 days, max 120 mg/day but unclear if more helpful	Check baseline blood pressure, then every 3-6 months; serotonergic and noradrenergic effects at all doses; modest inhibition of CYP2D6, CYP1A2.MDD/GAD/Diabetic peripheral neuropathy/Fibromyalgia

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, Zyban®)	For bupropion, Wellbutrin, Zyban:Start: 75 mg po bid or 100-150 mg q am and increase to 100-150 mg bid (2nd dose in afternoon) after 4-7 days, different dosing for different formulations	Contraindicated in patients with history of seizure, eating disorder or if otherwise at high seizure risk; least likely to cause sexual side effects or weight gain; modest inhibition of CYP2D6.MDD/Prevention of MDE in patients with seasonal affective disorder/Aid to smoking cessation treatment
Mirtazapine(Remeron®)	Start: 7.5-15 mg po qhs and increase to 30 mg q hs after 4-7 days, max 45 mg po qhs	Improves appetite and sleep as early side effects; low risk of medication interactions; less sexual side effects than SSRIs; may be more sedating at lower doses; may work faster than other antidepressants.MDD
Trazodone(Desyrel®)	For insomnia only:Start: 25 mg po qhs, if needed increase to 50 mg, then can increase by 50 mg increments up to 200 mg at bedtime	Used primarily for insomnia; may cause orthostasis, priapism; no longer used as antidepressant but when used as antidepressant dose was 400 mg daily; CYP3A4 substrate.Depression

- ® Generic and U.S. brand name(s).
- Dosing should be adjusted downwards ("start low, go slow" strategy) for the elderly and/or the medically compromised.
- Abbreviations: bid-(bis in die) twice a day; CYP-Cytochrome P450 enzyme; FDA-Food and Drug Administration; GAD-Generalized Anxiety Disorder; MAOI-Monoamine Oxidase Inhibitor; MAO-B-Monoamine Oxidase Inhibitor, B subtype; MDD-Major Depressive Disorder; MDE-Major Depressive Episode; mg-milligram; ng/mL-nanogram per milliliter; OCD-Obsessive Compulsive Disorder; PMDD-Pre-menstrual Dysphoric Disorder; po-(per os) orally; PTSD-Post-traumatic Stress Disorder; q-(quaque) every; qhs-(quaque hora somni) at bedtime; SNRI-Serotonin Norepinephrine Reuptake Inhibitor; SSRI-Selective Serotonin Reuptake Inhibitor; TCA-Tricyclic Antidepressant; WHO-World Health Organization.

16.2 Anxiolytics

The pharmacological treatment of anxiety symptoms is both simple and complicated. On the one hand, medications such as benzodiazepines and barbiturates can have a relatively immediate effect on distressing anxiety symptoms. On the other hand, the use of such medications carries the risk of cognitive impairment, physical dependence, as well as the risk of psychological dependence and inappropriate use in some patients.

It is not clear that episodic anxiety that is associated with situational stressors should be treated with medications. Anxiety per se may be a normal response to distressing events and a signal that may enhance a person's motivation to address these real-life events. As such, it may be better understood and addressed through psychotherapy rather than pharmacologically. Medical students and physicians should be aware of cultural (and managed care) pressures that push for "popping a pill" rather than addressing the underlying causes of the patient's anxiety and improving coping strategies.

Anxiety disorders are characterized by persisting patterns of anxiety symptoms impairing functioning. Examples include panic disorder, social anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder and generalized anxiety disorder. The first-line medication treatments for most anxiety disorders are SSRIs (or other antidepressants with serotonergic effects—see Table 1). A time period of several weeks may be necessary before clear response. During this time, anxiolytics with more immediate effects (e.g., benzodiazepines) may be used for early symptom control.

16.2.1 Benzodiazepines

Benzodiazepines were first developed in the 1960s and are now the most commonly used anxiolytics used in the United States. Diazepam, clonazepam, chlordiazepoxide, temazepam, oxazepam, lorazepam, and alprazolam are examples of benzodiazepines. Their mechanism of action is through their binding on ?-aminobutyric acid (GABA) receptors.(Nutt and Malizia 2001) GABA is the primary inhibitory neurotransmitter in the brain. Benzodiazepines bind to one type of GABA receptor (GABAA) thereby increasing the receptor's affinity for GABA. Increased GABA effect then increases the frequency of chloride channel openings allowing this ion's influx into the cell which in turn decreases normal cell firing. The benzodiazepine binding site is composed of multiple subunits; binding to the alpha-1 subunit may explain sedative effects of benzodiazepines whereas alpha-2 subunit binding may be needed for anxiolytics effects.(Nestler, Hyman et al. 2009)

Benzodiazepines are associated with multiple adverse effects. They are sedating, can impair concentration, memory,(Buffett-Jerrott and Stewart, 2002) coordination, can lead to falls in the elderly(Wagner, Zhang et al. 2004) (especially at initiation of treatment and after dose increases), and can cause respiratory depression. The choice of which benzodiazepine to use is often based on the pharmacokinetics of each drug. Diazepam, chlordiazepoxide, and clonazepam have relatively long half-lives. Additionally, diazepam and chlordiazepoxide are significantly hepatically metabolized and have multiple active metabolites; the use of these medications in hepatically compromised patients is therefore problematic. In medically ill patients, and in the elderly, benzodiazepines with short half-lives, such as lorazepam and oxazepam, are preferred, especially when the risk of respiratory depression is a concern (e.g.,

patients with chronic obstructive pulmonary disease). Alprazolam has a shorter half-life than lorazepam and oxazepam. It is, however, also associated with significant rebound anxiety because of the rapid drop from peak serum level after each dose. Despite its current widespread use, alprazolam should generally be avoided in patients who may require frequent or daily administration of an anxiolytic drug.

Perhaps the greatest drawback of benzodiazepines, however, is that they can lead to abuse and/or dependence. Physical dependence is characterized by increased tolerance to these drugs and the development of significant withdrawal symptoms upon discontinuation; this occurs with long term and/or high dose use of benzodiazepines and is not necessarily a sign of misuse or addiction (although patients should be made aware of the need for very gradual taper of these medications if used long term). Addiction, on the other hand, which may include elements of physical dependence, is characterized by maladaptive behavioral changes leading to medication misuse. Benzodiazepines (along with barbiturates discussed below) are controlled substances which should be prescribed judiciously and cautiously and only when adequate follow-up is available to ensure appropriate use. It should be noted that adequate follow-up is not often feasible in primary care settings. Benzodiazepines should generally be avoided in any patient with a history of substance or alcohol abuse: most benzodiazepine abuse or dependence occurs in these individuals. Admittedly, there are circumstances in which a patient with a history of substance abuse may require benzodiazepines (e.g., a patient with a severe debilitating panic disorder who has been refractory to all other non-benzodiazepine medications)—these circumstances, however, should be considered infrequent.

16.2.2 Barbiturates

Developed in the 1940's and 50's, barbiturates are now rarely used for the treatment of anxiety due to a higher risk of dependence and dangerousness in overdose when compared to benzodiazepines. Whereas benzodiazepine binding increases the receptor's affinity for GABA and indirectly affects chloride channels, barbiturates (and alcohol), binding on a different site on GABAA receptors, can increase chloride influx into neurons even when GABA is not present. Chloral hydrate, a weak barbiturate, is still occasionally used in certain settings for the treatment of refractory insomnia or for sedation prior to anxiety provoking medical studies (e.g., MRI). Other barbiturates such as phenobarbital, pentobarbital, and butalbital, are still commonly used in other areas of medicine for treatment of conditions (e.g., seizure disorder, pain) other than anxiety disorders.

16.2.3 Medicines without Abuse Potential Used for the Treatment of Anxiety

Buspirone is a partial 5HT1A agonist (primarily on autoreceptors) causing decreased serotonin release from serotonergic neurons. It is not clear why this action would help decrease anxiety; any effect is presumed to be due to "downstream" adaptations over several weeks. Buspirone has no effect on GABA receptors and as such cannot immediately replace benzodiazepines. It has no immediate anxiolytic effects. However, it has no potential for abuse, and does not impair cognition or motor coordination. Side effects, however, may

include headache, insomnia, jitteriness and nausea. It is indicated for the treatment of Generalized Anxiety Disorder.

Propranolol is a beta-adrenergic antagonist. Although it is primarily used medically for its effect on heart rate and blood pressure, its "off-label" use in psychiatry is based on its ability to reduce overall sympathetic activation. It is particularly helpful in circumstances where a sympathetic reaction to an anxiety-provoking stimulus can occur, such as in instances of performance anxiety. Musicians, for example, may take a dose one hour prior to their appearance on stage. Propranolol can decrease somatic manifestations of anxiety such as tremulousness and tachycardia. It does not, however, help alleviate symptoms associated with generalized social phobia or generalized anxiety disorder. Propranolol should be avoided if the patient has congestive heart failure or significant asthma. Despite earlier concerns that beta-blockers may cause depression (Waal, 1967) this is not supported by more recent studies.(Ko, Hebert et al. 2002)

Clonidine, initially developed as an antihypertensive, is an alpha-2-adrenergic autoreceptor agonist which serves to decrease sympathetic drive in the locus ceruleus. It can decrease hyperarousal in patients with post-traumatic stress disorder (Boehnlein and Kinzie, 2007) and other conditions associated with autonomic hyperactivity (e.g., rebound hyperactivity in opioid withdrawal states).

Prazosin is an alpha-1-adrenergic receptor antagonist. Like clonidine, it is an antihypertensive which can decrease anxiety symptoms associated with post- traumatic states. It has no sedative properties but it can help decrease PTSD symptoms during the day and decrease associated sleep disturbances and nightmares at night.(Miller, 2008; Raskind, Peskind et al. 2007; Taylor, Lowe et al. 2006; Taylor, Martin et al. 2008)

Hydroxyzine is an antihistamine with less affinity for muscarinic and alpha-1-adrenergic receptors than other antihistamines. Because it does not cause dependence and has no abuse potential, it is useful for treating anxiety symptoms in patients with a history of substance abuse. Also, it has been shown to have efficacy in the treatment of generalized anxiety disorder.(Llorca, Spadone et al. 2002; Lader and Scotto, 1998; Ferreri, and Hantouche et al. 1994)

16.2.4 Newer Hypnotics

Zolpidem, zaleplon, and eszopiclone (enantiomer of zopiclone which is available in Europe) are newly developed non-benzodiazepine hypnotics that bind to alpha-1 subunits on the benzodiazepine binding site on GABA receptors.(Sanger, 2004) These "z-drugs" cause sedation but lack anxiolytic effects despite some cross-reactivity with benzodiazepines. Although their abuse potential is purportedly less than benzodiazepines, they are not free from the risk of dependence and withdrawal symptoms upon discontinuation.(Cubala and Landowski, 2007; Liappas, Malitas et al. 2003; Sethi and Khandelwal, 2005; Victorri-Vigneau, Dailly et al. 2007) There is insufficient evidence that these hypnotics are either safer or more effective than benzodiazepines, yet, due to physician misconceptions, they have been widely used when more cost-effective treatments should be considered.(Siriwardena, Qureshi et al. 2006; Glass, Lanctot et al. 2005) Zolpidem is now generic, but zaleplon and eszopiclone are still brand products and are expensive. Ramelteon is a new hypnotic that is a melatonin receptor agonist which may have modest efficacy in shortening sleep

latency.(Sateia, Kirby-Long et al. 2008; Roth, Seiden et al. 2006) It is well-tolerated (Johnson, Suess et al. 2006) but again there are no studies to suggest it should be favored over more cost-effective alternatives. When considering treatment of chronic insomnia, physicians should not overlook the benefits that may be derived from nonpharmacological, e.g., behavioral, therapies.(Sivertsen, Omvik et al. 2006)

Table 2 summarizes the characteristics of selected non-antidepressant medications for the treatment of anxiety and insomnia.(WHO 2007; PDR 2008; Hyman, Arana et al. 1995; Rosenbaum, Arana et al. 2005; Stahl, 2005; Taylor, Paton et al. 2007) Antidepressants used in the treatment of anxiety disorders are listed in Table 1.

TABLE 2. SELECTED NON-ANTIDEPRESSANT MEDICATIONS FOR THE TREATMENT OF ANXIETY AND INSOMNIA

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Clonazepam (Benzodiazepine) (Klonopin®)	Start: 0.5 mg po bid for panic disorder, increase as needed, use lowest effective dose. Equivalence: 0.25 mg equals lorazepam 1 mg	Benzodiazepine with convenient pharmacokinetics for the treatment of panic disorder (30-50 hours half-life); CYP3A4 substrate.Panic disorder/Specific seizure disorders (see package insert)
Diazepam (Benzodiazepine) (Valium®, Diastat®, Diazepam Injection®)	For oral diazepam, Valium: Start: 2 mg po bid-tid, increase as needed, use lowest effective dose. Equivalence: 5 mg equals lorazepam 1 mg	Rapid onset of action followed by rapid distribution to lipid compartment, long elimination half-life. On WHO Essential Medicines List for generalized anxiety and sleep disorders, and as an anticonvulsant.Anxiety disorders and symptoms/Alcohol withdrawal symptoms/Adjunctive treatment for convulsive disorders/Adjunctive therapy in skeletal muscle spasms

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Chlordiazepoxide (Benzodiazepine) (Librium®)	Start: 10 mg po tid-qid, increase as needed, use lowest effective dose. Equivalence: 25 mg equals lorazepam 1 mg	Frequently used in inpatient detoxification for alcohol withdrawal symptoms when there is no hepatic dysfunction; multiple psychoactive metabolites.Anxiety disorders and symptoms/Alcohol withdrawal symptoms/Preoperative anxiety and apprehension
Oxazepam (Benzodiazepine) (Serax®)	Start: 10 mg po tid, increase as needed, use lowest effective dose. Equivalence: 15 mg equals lorazepam 1 mg	Used in inpatient detoxification when hepatic impairment is present; slowest onset of action among benzodiazepines.Anxiety Alcohol withdrawal
Lorazepam (Benzodiazepine) (Ativan®, Ativan Injection®)	For oral lorazepam, Ativan: Start: 0.5 mg po bid-tid, increase as needed, use lowest effective dose	Most widely used in inpatient setting for "as needed" treatment of anxiety, agitation, and withdrawal states; only benzodiazepine available IM.Anxiety Disorders and symptoms/Status epilepticus (for injection)/Preanesthetic medication for adults (for injection)
Alprazolam (Benzodiazepine) (Xanax®, Xanax XR®, Niravam®)	For alprazolam, Xanax, Niravam: Usual starting dose is 0.25 mg po tid, change to other benzodiazepine if ongoing treatment is needed. Equivalence: 0.5 mg equals lorazepam 1 mg	Most addictive benzodiazepine; infrequent "as needed" use may be appropriate; CYP3A4 substrate.Anxiety disorders and symptoms/Panic disorder
Buspirone (Atypical anxiolytic) (Buspar®)	Start: 5 mg po bid-tid; increase every 2-3 days by 5-10 mg to 30-40 mg in two divided doses, maximum dose is 60 mg/day	Alcoholics with anxiety may require near maximum doses; CYP3A4 substrate.Anxiety disorders and symptoms corresponding to GAD

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Propranolol (Beta-blocker) (Inderal®, Inderal LA, Innopran XL®)	For propranolol, Inderal: Start: test dose of 10 mg po, then up to 40 mg 0.5-1 hour before anxiety provoking event	Also used in psychiatry to treat akathisia, lithium-induced tremor, and clozapine- induced tachycardia.Migraine prophylaxis/ Hypertension/Other cardiac conditions (see package insert)
Clonidine (Antihypertensive) (Catapres®, Catapres-TTS®)	For oral clonidine, Catapres: Start: 0.1 mg po bid-tid or qhs, increase as needed and tolerated	Also used for opiate withdrawal.Hypertension
Prazosin (Antihypertensive) (Minipress®)	Start: 1 mg po qhs, after 3 days increase to 2 mg po qhs, after 4 more days increase to 4 mg po qhs, if no response after 7 days then increase to 6 mg po qhs, after another 7 days increase to 4 mg po at 3 pm and 6 mg po qhs	Helpful for insomnia and nightmares associated with PTSD.Hypertension
Hydroxyzine (Antihistamine) (Atarax®, Vistaril®)	Start: 10-12.5 mg po bid and 20-25 mg po qhs, increase as needed and tolerated	May also have analgesic effects; antiemetic, antihistamine, may help with insomnia.Anxiety symptoms/Multiple other indications(see package insert)
Zolpidem (Hypnotic) (Ambien®, Ambien-CR®)	For Ambien: Start: 5 mg po qhs, may increase to 10 mg po qhs if needed	Rapid onset; reported cases of amnesia; sertraline may increase serum level.Short-term treatment of insomnia characterized by difficulties with sleep initiation
Zaleplon (Hypnotic) (Sonata®)	Start: 5 mg po qhs, may increase to 10 mg qhs, maximum 20 mg po qhs	Amnesia may occur as it does with benzodiazepines; ultra-short half-life; expensive; CYP3A4 substrate.Short-term treatment of insomnia

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Eszopiclone (Hypnotic) (Lunesta®)	Start: 1-2 mg po qhs, maximum 3 mg po qhs	Amnesia may occur; similar dependence potential to diazepam; expensive with no advantages; CYP3A4 substrate.Treatment of insomnia
Ramelteon (Melatonin receptor agonist) (Rozerem®)	8 mg po within 30 minutes of bedtime, do not take with fatty meal	No DEA restriction; very short half-life; expensive; CYP1A2, CYP2C9, and CYP3A4 substrate.Treatment of insomnia characterized by difficulty with sleep onset

- ® Generic and U.S. brand name(s).
- Dosing should be adjusted downwards ("start low, go slow" strategy) for the elderly and/or the medically compromised.
- Abbreviations: bid-(bis in die) twice a day; CYP-Cytochrome P450 enzyme; DEA-Drug Enforcement Administration; FDA-Food and Drug Administration; IM-intramuscular; mg-milligram; po-(per os) orally; PTSD-Post-traumatic Stress Disorder; qhs-(quaque hora somni) at bedtime; qid-(quater in die) four times a day; tid-(ter in die) three times a day; WHO-World Health Organization.

16.3 Antipsychotics

16.3.1 First Generation Antipsychotics (FGAs)

The first antipsychotic, chlorpromazine, was developed in the 1950s.(Meyer and Simpson 1997) Subsequently other antipsychotics were developed that share similarities in their mechanisms of action and in their side effect profiles. Chlorpromazine, thioridazine, perphenazine, molindone, thiothixene, pimozide, fluphenazine, and haloperidol are examples of these medications which are now characterized as "first generation antipsychotics" (FGAs). Alternative names for this class of medications include: "neuroleptics" (for their propensity to cause adverse neurological effects), "major tranquilizers" (as opposed to the later designated "minor tranquilizers" such as benzodiazepines and barbiturates), "typical" antipsychotics, and "conventional" antipsychotics.

All first generation antipsychotics are believed to exert their antipsychotic effects through post-synaptic D2 dopamine receptor antagonism, thereby reducing the effect of endogenous dopamine released by presynaptic dopaminergic neurons.(Nestler, Hyman et al. 2009) Dopaminergic neurons originate from 3 distinct nuclei. One group of dopaminergic neurons projects from the ventral tegmental area of the midbrain to the nucleus accumbens, cingulate cortex and prefrontal cortex (the mesolimbic and mesocortical tracks); these affect emotions and cognition and as such are the targets for the therapeutic effects of antipsychotic drugs.

Dopaminergic neurons also arise from the substantia nigra and project to the striatum (the nigrostriatal track); these are implicated in the neurological side effects of antipsychotics. And finally, hypothalamic dopaminergic neurons project to the pituitary gland and serve to regulate the release of prolactin (the tuberoinfundibular track); disruption of this system with D2 blockade can result in hyperprolactinemia associated with the use of antipsychotics. Overall, in terms of clinical use, it has been shown that the optimal D2 receptor occupancy level for maximizing antipsychotic effect while minimizing adverse effects is 60-70%.(Farde, Nordstrom et al. 1992)

FGAs have traditionally been divided into low potency (e.g., chlorpromazine, thioridazine), mid-potency (e.g., perphenazine, molindone, thiothixene), and high potency (e.g., haloperidol, fluphenazine) antipsychotics, based on the number of milligrams of each drug needed to show comparable efficacy. For example, chlorpromazine 300 mg (low potency) may have the same therapeutic effect as perphenazine 24 mg (mid-potency) and haloperidol 6 mg (high potency). FGAs are often listed as a spectrum from low to high potency. The low potency antipsychotics usually exhibit TCA-like side effects such as anticholinergic, antihistaminic, and orthostatic effects (see section on antidepressants) but have a lower risk of causing acute neurological side effects such as acute muscle dystonias. At the other end of the spectrum, high potency FGAs have lower risks of TCA-like adverse effects but a much higher risk of causing acute dystonias. Mid-potency antipsychotics share all these side effects but less so than those of either pole. Physicians should become familiar with using at least one antipsychotic from each potency class in order to be able to match the side effect profile to the patient's pre-existing vulnerabilities.

When dosing FGAs, it is important to consider that although in most efficacy studies the presumed therapeutic dose of haloperidol is 10 mg/day, the ideal dose may be much lower: haloperidol 2 mg/day in neuroleptic-naïve patients, and 4 mg in non-neuroleptic-naïve patients may be sufficient to produce a "neuroleptic threshold"—the dose at which cogwheel rigidity, a sign of sufficient D2 receptor blockade, first appears.(McEvoy, Stiller et al. 1986)

The propensity of FGAs to cause neurological symptoms such as acute muscle dystonias, parkinsonism, akathisia, and tardive dyskinesia significantly limits their use in current practice. Acute dystonias, which are more likely to occur if the patient is young, male, has a history of substance abuse and/or a prior history of dystonias, is primarily seen in patients taking FGAs although it can also occur in patients with any antipsychotic with significant D2 receptor antagonism (see risperidone below). Use of anticholinergic medications, such as benztropine or diphenhydramine (or promethazine used outside the U.S.) can decrease the occurrence of early dystonias. Parkinsonism, characterized by bradykinesia, tremor, rigidity, and masked facies, can develop after 1-4 weeks of treatment with FGAs. Anticholinergic medications or a dopamine releasing agent such as amantadine may be helpful, although changing the antipsychotic may be required. Akathisia, which is an unpleasant subjective sense of inner restlessness relieved by movement, is also commonly seen in patients treated with FGAs. Identifying akathisia as a cause of agitation (or even worsening psychosis or suicidality) is important because treatment would include decreasing, rather than increasing, antipsychotic dose. Tardive dyskinesia (TD), a potentially irreversible syndrome of abnormal involuntary movements, can develop with extended use of antipsychotics, especially if high doses are used for long periods of time. Patients with prolonged antipsychotic treatment, a history of affective disorders, a history of parkinsonian side effects with initial antipsychotic treatment, as well as women and the elderly, are at a higher risk for developing TD. Once

tardive dyskinesia has developed, withdrawal of the antipsychotic (especially if this is precipitous) may unmask worsened abnormal movements. Resumption of antipsychotic treatment may suppress these symptoms for a period of time, but progression of the underlying movement disorder may continue. Despite trials of multiple remedies, treatments for TD are generally only partially effective.(Soares-Weiser and Fernandez 2007)

Neuroleptic malignant syndrome (NMS), is a poorly understood, rare, but potentially fatal complication of treatment with FGAs and other antipsychotics. NMS is characterized by a constellation of symptoms which may include delirium, lead-pipe rigidity, autonomic instability and high fevers. It can develop very early in the course of antipsychotic treatment. A high serum creatine phosphokinase (CPK) and elevated white blood cell count are supportive of the diagnosis of NMS. If NMS appears likely then the offending antipsychotic should be immediately discontinued. Medical hospitalization is necessary and treatment may include the use of a dopamine agonist (e.g., bromocriptine), a muscle relaxant (e.g., dantrolene), aggressive hydration, and the use of benzodiazepines if needed for behavioral agitation.(Hu and Frucht, 2007) Once the patient has been medically stabilized, the offending agent should be avoided. Rechallenge may be possible two weeks after all symptoms of NMS have abated, optimally with a low potency antipsychotic.

16.3.2 Second Generation Antipsychotics (SGAs)

Second generation antipsychotics, also known as atypical antipsychotics, are believed to exert their antipsychotic effects through a similar mechanism of action, but have profiles of receptor activity that produce different side effects than FGAs. The first SGA to be developed was clozapine, which was followed by the sequential introduction of risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole in the U.S. (and amisulpride and zotepine among others, in other countries). Whereas FGAs were known to (1) possibly worsen (or at least not improve) the negative symptoms of schizophrenia and (2) cause extrapyramidal symptoms including TD, SGAs were hoped to be more effective in treating negative symptoms and less likely to cause movement disorders. It is true that, by and large, SGAs do not worsen negative symptoms of schizophrenia and have a much lower risk of causing TD.(Correll, Leucht et al. 2004) However, questions regarding the differential effectiveness of SGAs as compared with FGAs, and their greater risks of inducing other, non-neurological, adverse effects have served to dampen the optimistic expectations initially associated with the medications. Nevertheless, in most of the world where they are available, SGAs are still considered to be the first line for treatment of psychotic disorders.

Risperidone, one of the earliest SGAs to be developed, was released in 1994. It is similar to FGAs in that it is a potent D2 receptor antagonist, but like many other SGAs, it is also a post-synaptic serotonin 5HT2A antagonist. This is thought to mitigate the D2 receptor-mediated neurological side effects. At doses lower than 6 mg/day (i.e., at usual therapeutic doses), risperidone carries a low risk of causing EPS; at higher doses, D2 blockade effects predominate and the risk of EPS increases significantly. EPS are usually not present at risperidone 3 mg/day—a dose at which 72% of D2 receptors are occupied.(Nyberg, Eriksson et al. 1999) The optimal dose derived from clinical studies appears to be 3-6 mg daily.(Osser and Sigadel, 2001) Although generally a well-tolerated antipsychotic, the side effects of risperidone include possible hypotension and hyperprolactinemia, and in children and adolescents it produces considerable weight gain.(Sikich, Frazier et al. 2008) It is

a hepatic CYP2D6 enzyme substrate and therefore its metabolism can be slowed by (1) inhibitors such as fluoxetine and paroxetine,(Spina, Scordo et al. 2003) or (2) the CYP2D6 variant gene for slow metabolism, which results in a less active form of the CYP2D6 enzyme (found more often in Chinese and other East Asian individuals).(Bertilsson, 1995) Another gene variant that causes "poor" metabolism is more common in Caucasians and results in severe side effects. On the positive side, risperidone has a low to medium propensity to cause adverse metabolic effects in adults (see discussion below). It may also have a somewhat more rapid onset of action compared to other second generation antipsychotics.(Osser and Sigadel, 2001) The newly introduced (and therefore more costly) paliperidone, which is the major active metabolite of risperidone with similar efficacy and similar side effect profile, is not metabolized by CYP2D6 and is mostly renally excreted.

Olanzapine was introduced in 1996. It has less affinity for D2 receptors than risperidone and a greater affinity for 5HT2A and 5HT2C serotonin receptors. Olanzapine also has significant antihistaminic and anticholinergic effects. Although it is an effective antipsychotic for the treatment of schizophrenia (especially at doses equal or greater than 15 mg/day),(Osser and Sigadel, 2001) it is (along with clozapine as discussed below) associated with a high risk of developing weight gain, insulin resistance, and hyperlipidemia (i.e., "metabolic syndrome"). Concern about the increased morbidity and mortality associated with the metabolic syndrome has lead to a reduction of the use of olanzapine in recent years. All side effects increase when olanzapine is used at higher than recommended doses (e.g., 40 mg/day vs. the package insert maximum dose of 20 mg/day) with very little additional antipsychotic benefit.(Kinon, Volavka et al. 2008) Liver transaminases can also become transiently elevated with olanzapine.

Quetiapine shows weak affinity at both dopamine and 5HT2 serotonin receptors, but may have similar receptor occupancy to the more potent SGAs.(Seeman, 2002) It has alpha-adrenergic antagonism and antihistaminic effects, causing orthostasis and sedation, respectively. Quetiapine is less likely than olanzapine and clozapine, but more likely than most FGAs, risperidone and other SGAs, to cause metabolic side effects. Quetiapine, at low doses, is widely (and perhaps too readily) used in psychiatric practice for the treatment of insomnia and acute anxiety in a wide range of patients with personality and/or substance abuse disorders for whom benzodiazepine use may be problematic. This "off-label" use should only be carried out after a thoughtful review of risks, benefits, and alternative treatments, especially evidence-supported treatments, for patients' diagnosed conditions. Clinicians should be aware also of recent reports of abuse and "street value" for this medication.(Hanley and Kenna, 2008) Use of quetiapine for anxiety symptoms may be more appropriate in acute care settings such as during hospitalizations. Quetiapine's effectiveness in psychotic disorders may be less than that of olanzapine and risperidone,(McCue, Waheed et al. 2006; Suzuki, Uchida et al. 2007) but it may have a stronger role in bipolar disorders (see section on mood stabilizers).

Ziprasidone is an SGA with moderate D2 antagonism and significant 5HT2A antagonism (i.e., a high 5HT2A/D2 ratio). Although it is not clear if it is as effective as olanzapine and risperidone in the acute treatment of schizophrenia,(McCue, Waheed et al. 2006) it does not cause metabolic changes, and may even improve lipid profile, especially if the patient was previously on a weight gain-inducing agent.(Lieberman, Stroup et al. 2005) A major issue with using ziprasidone is the necessity of taking it with food, or it will not be well-absorbed. A 500 calorie meal is optimal with each of the twice daily doses.(Miceli, Glue et al. 2007)

Ziprasidone has the potential to prolong QT more than other SGAs. Although a pre-treatment ECG is not required, those who are deemed, based on history or age, to be at higher cardiac risk would benefit from an ECG (and medical consultation if appropriate) before starting ziprasidone. Electrolyte disturbances such as hypomagnesemia and hypokalemia should be corrected. Other QT prolonging medications should not be used in combination with ziprasidone. Despite concerns regarding this effect, post-marketing studies (e.g., CATIE)(Lieberman, Stroup et al. 2005) did not show any clinically significant QT prolongation with ziprasidone use.

Medical students and physicians should be aware that all antipsychotics (with the possible exception of aripiprazole discussed below) can affect cardiac conduction, potentially delaying conduction enough to lead to fatal arrhythmias. There is an association between the use of antipsychotics (as well as tricyclic antidepressants) and sudden death.(Ray, Chung et al. 2009; Ray, Meredith et al. 2004; Straus, Bleumink et al. 2004) As discussed in the section on antidepressants, prolonged QTc is associated with torsades de pointes, a potentially fatal arrhythmia. The QT interval includes both the QRS interval as well as the ST segment. Whereas TCAs and some FGAs with tricyclic structure (e.g., chlorpromazine) lengthen the QRS interval by interfering with sodium channels and depolarization, most other antipsychotics, including SGAs, can affect potassium channels and the repolarization phase.(Glassman and Bigger, 2001) Both effects would be reflected in the QT interval. Although it is not clear if QT prolongation is actually a reliable indicator of the risk of torsades, measuring this interval is the simplest way to estimate this risk.(Shah, 2005) In addition to ziprasidone, the FGAs thioridazine, mesoridazine, pimozide, and droperidol are among the antipsychotics with the highest propensity to prolong the QT interval.(Fayek, Kingsbury et al. 2001)

Aripiprazole, in contrast to other SGAs, is a high affinity partial agonist at the D2 receptor.(Mamo, Graff et al. 2007) It is postulated that aripiprazole decreases overall dopamine effect(Stahl, 2008) in dopamine rich environments (e.g., in mesolimbic pathways--thereby ameliorating psychosis), and increases dopamine effect in dopamine depleted environments (e.g., in mesocortical pathways to the prefrontal cortex--thereby improving negative symptoms such as social withdrawal).(Stahl, 2008) At therapeutic doses it highly saturates the targeted dopamine receptors and shows very slow dissociation from the receptors upon discontinuation.(Goff, 2008; Grunder, Fellows et al. 2008) It also shows moderate 5HT2A and 5HT2C antagonism. On the other hand, it is free from anticholinergic and significant antihistaminic effects. More importantly, it does not appear to have significant cardiac or metabolic effects.(El-Sayeh, Morganti et al. 2006) Although it is less likely to cause EPS in general, it has been observed in practice to cause akathisia more readily than other SGAs. This side effect may be more common if the patient was recently on a strong D2 antagonist such as an FGA or risperidone and consequently has an up-regulated or hypersensitive population of D2 receptors.(Raja, 2007) Slow dose titration and/or combination with a benzodiazepine may be necessary to reduce the risk of akathisia.

Aripiprazole at 15 mg/day may be more efficacious than 30 mg/day in schizophrenia, although full response may take longer than with a comparable dose of haloperidol.(Kane, Carson et al. 2002) Higher doses (e.g., 30 mg/day) may be more useful in treatment-resistant schizophrenia.(Kane, Meltzer et al. 2007) Relapse rates may be somewhat higher with aripiprazole than with other SGAs.(Pigott, Carson et al. 2003)

Clozapine, the first and in some respects the most impressive of the second generation antipsychotics, binds weakly at the D2 receptor (although with relatively greater net antagonism at D3 and D4 dopamine receptors) and has moderate affinity for 5HT2A and 5HT2C receptors. It is often effective when other antipsychotics are not,(Lewis, Barnes et al. 2006) and appears to have antisuicidal effects in patients with schizophrenia or schizoaffective disorder.(Meltzer, Alphs et al. 2003) However, because of the risk of agranulocytosis, it is reserved primarily for schizophrenic and schizoaffective patients who have failed to respond adequately to at least two other antipsychotics. Strict monitoring and initially weekly and then biweekly blood draws are required to monitor white cell count. The clinician should consult the package insert and strictly follow the monitoring guidelines. Clozapine should not be combined with other medications (e.g., carbamazepine) that may also cause leukopenia.

Clozapine can also cause multiple other adverse effects, which include (but are not limited to) an increased risk of seizures, rare myocarditis, eosinophilia, anticholinergic and antihistaminic effects, orthostasis, weight gain and adverse metabolic effects.(Lamberti, Olson et al. 2006)

Among the SGAs, clozapine and olanzapine are the most likely (and aripiprazole and ziprasidone are the least likely) to cause adverse metabolic effects. These would include weight gain, hyperglycemia and diabetes (with or without weight gain) and hyperlipidemia.(ADA, 2004) A 2-3 kilogram weight gain within the first 3 weeks of treatment often predicts the risk of significant weight gain over the long term.(Lipkovich, Citrome et al. 2006) Decreased insulin secretion and increased triglycerides (i.e., the lipids most affected by SGAs)(Osser, Najarian et al. 1999) can also be seen within 1-2 weeks of treatment.(Chiu, Chen et al. 2006) Treatment with the hypoglycemic medication metformin, especially if combined with lifestyle changes, may reduce antipsychotic-induced weight gain.(Baptista, Rangel et al. 2007; Wu, Zhao et al. 2008)

Prior to starting olanzapine or clozapine, measurements of baseline weight, serum glucose, and lipid profile should be obtained. If the patient has pre-existing diabetes, other antispychotics should be considered. Once treatment is initiated, serum glucose and weight should be monitored and if glucose levels become elevated, a glucose tolerance test—which can predict up to 96% of patients who would develop diabetes—should be done.(van Winkel, De Hert et al. 2006) If metabolic problems do arise during treatment, switching to another antipsychotic should be considered.

Clozapine may cause orthostatic hypotension. Patients who are elderly, have cardiac histories, or who are taking antihypertensives are at higher risk for this side effect. Clozapine should be increased gradually after treatment is initiated (starting at 12.5 mg/day and increasing the dose by 25 mg daily as tolerated). Usually, patients adjust and become tolerant to the hypotensive effects of this medication. However, this tolerance may not last longer than 48 hours. If a patient discontinues clozapine therapy for more than 48 hours, treatment should be restarted with a 12.5 mg dose. After that, the dose may be more quickly raised to the previous dose as tolerated. It is important for the physician who may be admitting a psychiatric patient to the medical or surgical ward of the hospital to stop and think before continuing clozapine at its prior dose: recent compliance needs to be verified first.

Given the complicated nature of clozapine treatment, the clinician should refer to a more in depth discussion of this drug before use.(Phansalkar and Osser, 2009; Phansalkar and Osser. 2009)

16.3.3 Long-Acting Injectable Antipsychotics

In the United States, 3 antipsychotics are available for long-acting (i.e., depot) intramuscular administration: haloperidol decanoate, fluphenazine decanoate, and long-acting injectable risperidone. Olanzapine long-acting injection is expected to be approved soon. These long-acting formulations are options for patients who are frequently non-adherent to the prescribed oral medication.(Olfson, Marcus et al. 2007) A brief trial of the antipsychotic in oral form is first prescribed to assess patients' response to, and tolerance of, the selected agent. Every four week injections of haloperidol decanoate or biweekly injections of long-acting fluphenazine or risperidone are then continued while the oral agent is gradually tapered. Four to five repeated injection cycles of the selected antipsychotic may be necessary to achieve steady state before oral medications should be completely withdrawn.(Osser and Sigadel ,2001) Patients who adhere poorly to oral medications in real-world public sector settings are generally non-adherent to depot antipsychotics as well.(Olfson, Marcus et al. 2007) These formulations seem to work best in research subjects and in other populations of relatively cooperative and less treatment-resistant patients. On the other hand, once steady state is achieved, depots do have the advantage that if the patient discontinues treatment, the antipsychotic effect can continue for up to several months after the last received dose.

16.3.4 Antipsychotics for Behavioral Control

Both SGAs and FGAs are used in psychiatric practice to treat behavioral agitation. In acutely psychotic and/or manic patients, FGAs, such as oral or intramuscular haloperidol (often combined with lorazepam and/or benztropine to decrease the risk of acute dystonias), remain the mainstay of treatment.(Ansari, Osser et al. 2009, Osser and Sigadel, 2001) Newer antipsychotics, such as olanzapine, ziprasidone, and aripiprazole are also available in short-acting intramuscular form but they are expensive and seem to have no advantage when compared with the combination therapy noted above.(Satterthwaite, Wolf et al. 2008) When considering antipsychotics for behavioral agitation, clinicians should be advised not to use (1) intramuscular droperidol due to high risk of QT prolongation, (2) intramuscular chlorpromazine due to risk of severe hypotension, (3) intramuscular ziprasidone if the patient is taking other medications that can also prolong QT, or (4) intramuscular olanzapine in combination with lorazepam or other benzodiazepines due to the risk of hypotension.(Zacher and Roche-Desilets, 2005)

The use of antipsychotics for the treatment of behavioral agitation in elderly patients with dementia is problematic both in terms of effectiveness and tolerability. First, in terms of effect, they do not appear to provide more than minimal benefit in targeting symptoms of agitation, and SGAs may not be different from placebo in this regard.(Yury and Fisher, 2007) The NIMH-sponsored CATIE-AD study, which studied the effectiveness of olanzapine, quetiapine and risperidone in the treatment of symptoms of psychosis, aggression and agitation in patients with Alzheimer's disease, also found that even when these symptoms did improve with treatment, the antipsychotic did not improve overall functioning.(Sultzer, Davis et al. 2008) Furthermore, any improvement in specific symptoms was offset by adverse effects and led to overall discontinuation rates (when both efficacy and tolerability were considered) that were no different from placebo.(Schneider, Tariot et al. 2006) Secondly, antipsychotics have been found to be associated with an increased risk of stroke in patients

with dementia and an overall increased risk of adverse medical events and death in this population.(Gill, Rochon et al. 2005; Herrmann and Lanctot, 2005; Rochon, Normand et al. 2008; Schneider, Dagerman et al. 2005) Both FGAs and SGAs appear to increase the risk of death in patients with dementia.(Schneeweiss, Setoguchi et al. 2007; Wang, Schneeweiss et al. 2005)

High-potency FGAs are also often used in the treatment of delirium in hospitalized patients.(Lonergan, Britton et al. 2007) Medical students and physicians should be aware that although antipsychotics may treat the secondary manifestations of delirium, such as behavioral agitation and/or hallucinations, they do not treat the underlying condition. Delirium is a medical condition that is treated by addressing the underlying medical cause.

16.3.5 Further Notes on the Clinical Use of Antipsychotics

All antipsychotics are indicated for the treatment of schizophrenia and are considered reasonably safe and effective for this debilitating disorder. However, there has been much debate about whether there are efficacy differences among these medications, or whether the side effect differences, which are considerable, should be the primary basis for selecting a medication for a particular patient. A meta-analysis of 78 head-to-head comparisons in the literature through 2007 concluded that the efficacy differences are small, but there was some superiority to olanzapine and risperidone, when compared with aripiprazole, quetiapine, and ziprasidone. A problem with this meta-analysis, however, was that almost all of the studies were industry-sponsored. Such studies invariably find outcomes in favor of the sponsor's product, and olanzapine and risperidone have sponsored the largest number of studies.

Another meta-analysis focused on 150 studies that directly compared FGAs with SGAs.(Leucht, Corves et al. 2009) The authors found that clozapine was clearly superior to the others especially for positive symptoms of hallucinations and delusions. Olanzapine and risperidone were superior to the others, but with a small effect size. The others did not differ in efficacy. The side effect profiles differed markedly, with no pattern to the differences. The authors recommended abandoning the terms "FGA" and "SGA" as irrelevant to efficacy or side effects.

Many clinicians put more reliance on the relatively few comparison studies that were independently funded, such as the CATIE (Clinical Antipsychotics Trials of Intervention Effectiveness) and TEOSS (Treatment of Early-Onset Schizophrenia Spectrum Disorders) studies.(Lieberman, Stroup et al. 2005; Sikich, Frazier et al. 2008) Both were funded by the U.S. National Institute of Mental Health. These studies prospectively compared FGAs (perphenazine, molindone) and SGAs (clozapine, olanzapine, risperidone, quetiapine, ziprasidone) and found generally no differences in effectiveness except that clozapine was superior. There were no differences in the ability to improve impaired cognition, despite prior claims for SGA superiority from studies sponsored by the SGA pharmaceutical firms.(Keefe, Bilder et al. 2007)

Some experts have interpreted CATIE as showing olanzapine to be superior to the other non-clozapine antipsychotics, but this seems likely to be due to peculiar results with the cohort of patients who were on olanzapine prior to entering the CATIE study. These patients (22% of the sample) were randomly assigned to either continue on olanzapine or be switched to one of the other options in CATIE (perphenazine, risperidone, quetiapine, or ziprasidone).

The patients who were assigned to remain on olanzapine did better than those who were abruptly switched to any of the other options.(Essock, Covell et al. 2006) By contrast, the patients who entered the study on risperidone (the second largest group with 19%) showed no advantage to staying on risperidone compared to switching to another agent. Notably, there was no advantage to switching to olanzapine. Hence, the superiority of olanzapine seen in CATIE may be due to the study having a large sample of patients who had been previously stabilized on olanzapine and who clearly responded only to olanzapine or who may have been more prone to a withdrawal-induced exacerbation when taken off of olanzapine. Since olanzapine has a very unfavorable side effect profile with its tendency to promote weight gain, insulin resistance, and the metabolic syndrome, this would appear to make it undesirable as a first-line choice even if it does have slightly superior efficacy.

Antipsychotics are also being used in a wide variety of mood and anxiety disorders as augmentations when antidepressants produce unsatisfactory results, and sometimes they are used as primary treatments for these disorders. Recent data indicating that SGAs and FGAs are associated with double to triple the rate of death from sudden cardiac arrest (presumably from electrophysiological effects related to QT prolongation) suggest that these agents should not be first-line treatments in these clinical situations.(Ray, Chung et al. 2009) However, antipsychotics are powerful and important options in the treatment of schizophrenia and severe bipolar disorders and these new cardiac concerns should not deter clinicians for prescribing them appropriately for these patients. Obtaining a baseline ECG, and if abnormal obtaining another after dosage has been optimized, is a prudent risk-management approach given this new data.

Table 3 summarizes the characteristics of commonly used antipsychotics.(WHO, 2007; PDR, 2008; Hyman, Arana et al. 1995; Rosenbaum, Arana et al. 2005; Stahl, 2005; Taylor, Paton et al. 2007)

TABLE 3. COMMONLY USED ANTIPSYCHOTICS

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Chlorpromazine (FGA) (Thorazine®)	For oral: Start: 25-50 mg po qhs then increase as tolerated to 300 mg po qhs or in divided doses. Potency: 100 mg po equals haloperidol 2 mg po	Tricyclic structure therefore with TCA side effects, plus EPS; now rarely used as primary antipsychotic; avoid IM given risk of severe orthostasis. On WHO Essential Medicines List for psychotic disorders.Psychotic disorders/Other indications (see package insert)

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Thioridazine (FGA) (Mellaril®)	Start: 25 mg po q day/bid/tid for agitation in a variety of anxiety, mood, personality disorders; for schizophrenia increase the same as chlorpromazine. Potency: 80-100 mg po equals haloperidol 2 mg po	Was once the most frequently prescribed antipsychotic; now should avoid use due to one of the highest risks of QTc prolongation of all FGAs and SGAs; doses over 800 mg/day may cause pigmentary retinopathy; CYP2D6 substrate, avoid combining with CYP2D6 inhibitors or any SSRI or propranolol.Schizophrenia in patients not responsive to or intolerant to other antipsychotics
Perphenazine (FGA) (Trilafon®)	Start: 4 mg po bid then increase by 4-8 mg every 2 days; 20-24 mg/day in divided doses may be sufficient, 40 mg/day in treatment resistant patients, maximum dose 64 mg/day. Potency: 8-10 mg po equals haloperidol 2mg po	Effective in recent studies in comparison with SGAs; good choice for a first-line FGA.Schizophrenia
Molindone (FGA) (Moban®)	Start: 5 mg po bid and increase over several days to typical dose of 30-60 mg total per day, maximum dose 300 mg/day. Potency: 10 mg po equals haloperidol 2 mg po	Recently found to work well in study of adolescents in comparison with risperidone and olanzapine; no weight gain; akathisia is common.Schizophrenia
Pimozide (FGA) (Orap®)	Start: 0.5 mg po q day, increase very gradually if needed and maintain low doses (less than stated maximum of 10 mg/day). Potency: 1 mg po equals haloperidol 2 mg po	Avoid use; historically used for delusional parasitosis but no reason to believe better for this than others; high risk of QTc prolongation; CYP3A4 substrate.Suppression of refractory tics secondary to Tourette's Syndrome

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Fluphenazine (FGA) (Prolixin®)	For oral: Start: 0.5-2 mg po bid and increase as tolerated and necessary, usual daily dose is 5-10 mg/day. PO max is 40 mg/day IM max is 20 mg/dayOral dose is equipotent with haloperidol	Available in short-acting IM for behavioral control and long-acting injectable depot preparation for maintenance treatment of poorly adherent patients given every 2 weeks (see package insert); On WHO Essential Medicines List for psychotic disorders.Psychotic disorders
Haloperidol (FGA) (Haldol®)	For oral: Start: 0.5-2 mg po q day or bid and increase as tolerated and necessary, lower doses for elderly delirious patients and higher doses in patients with schizophrenia, 4-10 mg/day may be sufficient in schizophrenia	Most widely used FGA; also used for secondary symptoms of delirium and behavioral control; available in short-acting IM form for behavioral control and long-acting injectable depot form for maintenance treatment given every 4 weeks (see package insert); CYP2D6 substrate. On WHO Essential Medicines List for psychotic disorders.Psychotic disorders

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Risperidone (SGA) (Risperdal®, Risperdal M-Tab®, Risperdal Consta®)	For oral risperidone, Risperdal, Risperdal M-Tab: Start: 0.5-1 mg po bid and increase gradually every 1-2 days to target of 4 mg/day, if no response in 1-2 weeks then increase to 6 mg/day	Fairly well-tolerated SGA, no significant EPS under 4 mg/day, and medium to low risk of metabolic changes in adults; orthostasis may be a problem initially; hyperprolactinemia is common; may have more rapid action than other SGAs; available in long-acting injectable depot form for maintenance treatment given every 2 weeks (see package insert); CYP2D6 substrate.Schizophrenia/Psychotic disorders/Acute mania or mixed episodes/Irritability from autism (see package insert)
Olanzapine (SGA) (Zyprexa®, Zydis®, Zyprexa IntraMuscular®)	For oral olanzapine, Zyprexa, Zydis: Start: 15 mg/day for most rapid effect in male smokers for schizophrenia; 10 mg in women smokers; 5 mg in non-smoking women. May increase by 5 mg/-day until 15-20 mg/day, (package insert max is 20 mg/day although rarely doses up to 40 mg/day may be slightly better for treatment-resistant cases), see package insert for intramuscular use	Along with clozapine the highest risk of weight gain and metabolic syndrome among SGAs; CYP1A2, CYP2D6 substrate.Schizophrenia/Acute mania/Bipolar Maintenance

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Quetiapine (SGA) (Seroquel®, Seroquel XR®)	Start: 25-50 mg po bid and double daily until 100 mg bid then increase by 200 mg/day as tolerated depending on sedation and orthostasis to 600-800 mg/day, XR is once-daily version: 200 mg po qhs on day one, 400 mg po qhs on day 2, 600 mg po qhs on day 3	Efficacious in bipolar depression; used frequently off-label as anti-anxiety agent in substance abusers, and in personality disordered; CYP3A4, and CYP2D6 substrate.Schizophrenia/Acute mania/Bipolar depression/Maintenance treatment of bipolar I disorder as adjunct to lithium or divalproex
Ziprasidone (SGA) (Geodon®, Geodon for Injection®)	For oral: Start: 20-40 mg po bid and increase dose every 1-2 days to 80 mg po bid (need to take with food for adequate absorption—see text)	SGA with lowest risk of weight gain and metabolic side effects; has higher risk of QTc prolongation; available in short-acting IM form for behavioral control (see package insert); CYP3A4 substrate.Schizophrenia/Acute mania or mixed episodes
Aripiprazole (SGA) (Abilify®, Abilify Discmelt®)	For oral: Start: 2.5-5 mg po q am and increase every 2-3 days as tolerated to 15 mg/day, maximum is 30 mg/day but 15 mg/day may be more effective in acute schizophrenia; in mania 15 mg and 30 mg appear equally effective	SGA with low risk of cardiac and metabolic effects; however akathisia is common; very long half-life; available in short-acting IM form for behavioral control (see package insert); CYP2D6 and CYP3A4 substrate.Schizophrenia/Acute and maintenance treatment of mania and mixed episodes/ Adjunctive therapy to antidepressants for acute treatment of MDD

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Clozapine (SGA) (Clozaril®, Fazaclo®)	Start: 12.5 mg po once or twice daily then increase by 25 mg/day in divided doses as tolerated to 200-400 mg/day and check for response (check serum level if no response—therapeutic serum level of clozapine is over 350 ng/mL, some studies suggest over 450 ng/mL), need to restart at 12.5 mg/day if discontinued 48 hours or more	Risk of agranulocytosis; need WBC/ANC count and ECG before treatment; needs ongoing WBC monitoring-see package insert for WBC monitoring guidelines; multiple other risks; along with lithium may be one of only two drugs with antisuicidal effects; use caution when using with benzodiazepines; do not combine with carbamazepine; CYP1A2, CYP2D6, CYP3A4 substrate.Treatment resistant severe schizophrenia/Reduction of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder

- ® Generic and U.S. brand name(s).
- Dosing should be adjusted downwards ("start low, go slow" strategy) for the elderly and/or the medically compromised.
- Abbreviations: ANC-Absolute Neutrophil Count; bid-(bis in die) twice a day; CYP-Cytochrome P450 enzyme; ECG-Electrocardiogram; EPS-Extra-pyramidal Symptoms; FGA-First Generation Antipsychotics; IM-intramuscular; MDD-Major Depressive Disorder; mg-milligram; ng/mL-nanogram per milliliter; po-(per os) orally; q-(quaque) every; qhs-(quaque hora somni) at bedtime; SGA-Second Generation Antipsychotics; TCA-Tricyclic Antidepressants; WBC-White Blood Cell; WHO-World Health Organization.

16.4 Mood Stabilizers

What is a mood stabilizer? Although there is no generally accepted definition, a mood stabilizer can be defined as a medication that can treat either phase of bipolar disorder while not inducing or worsening the other phase. More conservatively, however, a mood stabilizer can be defined as an agent that can both treat and prevent both manic and depressive episodes. By this definition only lithium qualifies as a true mood stabilizer.(Bauer and Mitchner, 2004)

Lithium (as a salt) has been used as a homeopathic treatment for gout and other disorders since the 1800's. Its calming effect on animals, and subsequently on manic patients, was first described in the 1940s.(Cade, 1949) In the brain, lithium inhibits inositol phosphatases that

dephosphorylate inositol phosphates that are generated by the stimulation of G proteins in neuronal membranes activated by a neurotransmitter. This inhibition interferes with inositol regeneration and leads to its depletion in neurons, ultimately leading to decreased neuronal activity.(Nestler, Hyman et al. 2009) Lithium also inhibits protein kinases, glycogen synthase kinase-3beta, and adenylyl cyclase,(Bachmann, Schloesser et al. 2005; Lenox and Hahn 2000) and may increase the uptake of the excitatory neurotransmitter glutamate thereby reducing glutamate activity at the neuronal synapse.(Shaldubina, Agam et al. 2001) Lithium also appears to have neuroprotective properties and may promote neurogenesis.(Chuang, 2005; Chen and Manji, 2006; Bearden, Thompson et al. 2007; Nunes, Forlenza et al. 2007; Fornai, Longone et al. 2008)

Lithium is effective in both manic and depressive episodes associated with bipolar disorder, as well as for long-term maintenance. It is also the only mood stabilizer with anti-suicidal effect.(Baldessarini, Tondo et al. 1999; Cipriani, Pretty et al. 2005) Lithium works particularly well in patients who have a strong family history of bipolar disorder.(Alda, 1999)

A target therapeutic serum level of 0.6-0.75mEq/L is recommended for the treatment of bipolar depression and prophylaxis against depressive relapses.(Kleindienst, Severus et al. 2007; Kleindienst, Severus et al. 2005; Severus, Kleindienst et al. 2008) Serum levels of 0.75-1.2mEQ/L may be more effective for the treatment of mania. Serum levels higher than 1.2mEq/L are associated with significant lithium toxicity.

Lithium side effects usually increase with higher serum doses but can occur at any dose. These may include nausea, vomiting, diarrhea, tremor, thirst, polyuria, acne, weight gain, and a benign leukocytosis. Over the long run, lithium can cause hypothyroidism in up to 20% of patients(Johnston and Eagles 1999) (which can be treated with thyroid hormone replacement), and worsening renal function in 20% of patients (Lepkifker, Sverdlik et al. 2004) (which usually necessitates lithium discontinuation). Because of the many complexities of lithium use, access to references such as the Lithium Encyclopedia for Clinical Practice is recommended.(Jefferson, Greist et al. 1987)

Physicians should be aware that the anti-manic effects of lithium (and other mood stabilizers, such as valproate and carbamazepine, discussed below) may not be achieved until 7-10 days after a therapeutic dose has been established. In the interim, sedative medications such as antipsychotics and benzodiazepines may be needed when the patient is acutely manic. Once the patient is stabilized, these adjunctive medications can often be tapered and lithium continued as monotherapy.

Valproate (along with carbamazepine and lamotrigine discussed below) is an anticonvulsant with mood stabilizing properties. It is postulated that it exerts its effect via enhancement of GABA transmission.(Johannessen, 2000) Despite decades of clinical experience with lithium, valproate has become the most widely used mood stabilizer in the United States. This is primarily due to its ease of use and effectiveness in the treatment of mania. Valproate is not very effective in the treatment of bipolar depression, but has efficacy in the treatment of manic and mixed episodes (Bowden, Brugger et al. 1994; Freeman, Clothier et al. 1992) Although serum levels of 50-125 mcg/mL are generally considered to be within the therapeutic range (a range based on anticonvulsant data), the best results in acute mania may occur with levels of greater than 90 mcg/mL.(Allen, Hirschfeld et al. 2006) Side effects in adults include liver enzyme elevations (usually benign and transient, but not always), weight gain, and possible

thrombocytopenia and platelet dysfunction. Because of the latter, bleeding time should be measured prior to surgery even if the platelet count is normal.(De Berardis, Campanella et al. 2003; Gerstner, Teich et al. 2006) Valproate is highly protein-bound: concurrent use with warfarin can displace and increase the free fraction of warfarin and increase prothrombin time.

The use of valproate is problematic in women of child bearing age. It is associated with a high risk of teratogenic effects (i.e., neural tube defects).(Cohen, 2007; Viguera, Koukopoulos et al. 2007) Valproate may also play a role in the development of polycystic ovary syndrome.(Joffe, Cohen et al. 2006; O'Donovan, Kusumakar et al. 2002)

Many clinicians recommend the use of alternative medications, such as lithium in young bipolar women. Lithium can cause Ebstein's anomaly, an anomaly in the fetal tricuspid valve, at up to 3 times the baseline risk. Previously, this risk was thought to be much higher. For a more complete discussion of pregnancy risks of psychiatric medications, see the 2008 Practice Bulletin of the American College of Obstetrics and Gynecology.(ACOG, 2008)

Carbamazepine is an anticonvulsant that can enhance Na+ channel inactivation, thereby blocking action potentials and repetitive neuronal firing. It is also thought to inhibit a process known as kindling—a process whereby repeated subthreshold electrical stimuli can lead to the development of spontaneous seizures. Hypothetically, subthreshold environmental stimuli or prior manias can similarly kindle the development and frequency of further manias.(Rosenbaum, Arana et al. 2005)

Carbamazepine has efficacy in the treatment of manic (Weisler, Kalali et al. 2004; Weisler, Keck et al. 2005), but probably not depressive,(Ansari and Osser, 2009) episodes associated with bipolar disorder. Serum levels of 4-12 mcg/mL are considered to be therapeutic. Side effects such as dizziness, ataxia and gastrointestinal symptoms prohibit the use of loading strategies. Thrombocytopenia, leukopenia, hyponatremia, and dangerous rash may also develop with carbamazepine therapy. Another factor that significantly limits treatment with carbamazepine, especially in severe mania when concurrent antipsychotics may be necessary, is its propensity to induce multiple hepatic enzymes (e.g., CYP1A2, CYP2C9, CYP2C19, CYP3A4). It can therefore increase the metabolism of other concurrently administered drugs and render them less effective. (Notably, the antiepileptic drugs phenobarbital, phenytoin, and primidone also have similarly broad hepatic enzyme induction capacities.)(Perucca 2006) Teratogenic effects of carbamazepine are comparable in severity to those of valproate.(Cohen, 2007; Viguera, Koukopoulos et al. 2007)

Oxcarbazepine, an analog of carbamazepine, may also have efficacy in the treatment of acute mania.(Ghaemi, Berv et al. 2003; Pratoomsri, Yatham et al. 2006) Serum levels do not need to be checked, and there is less enzyme induction with oxcarbazepine, thereby reducing the risk of drug-drug interactions. Hyponatremia, however, remains a concern.(Ortenzi, Paggi et al. 2008)

Lamotrigine is an anticonvulsant that may inhibit the release of the excitatory amino acid glutamate, but its mechanism of action is not fully known. In bipolar disorder it is often used (but not FDA approved) for the treatment of bipolar depression. However, 4 out of 5 studies failed to show separation from placebo.(Calabrese, Bowden et al. 1999; Calabrese, Huffman et al. 2008) Nevertheless, it appears to be effective as maintenance therapy for depressive episodes in bipolar disorder.(Bowden, Calabrese et al. 2003; Calabrese, Bowden et al. 2003) Although lamotrigine is generally well-tolerated, there is a 0.1% risk of dangerous rash (i.e.,

toxic epidermal necrolysis—Stevens-Johnson syndrome). Gradual titration is required to decrease the risk of rash. If rash develops, lamotrigine should be discontinued. Lamotrigine so far seems relatively safe in pregnancy.(ACOG, 2008)

16.4.1 Second Generation Antipsychotics

All SGAs have been found to have efficacy in the treatment of mania.(Janicak, 2006) However, among the SGAs, only quetiapine has been shown to have clear efficacy in the treatment of bipolar depression.(Calabrese, Keck et al. 2005; Thase, Macfadden et al. 2006) Olanzapine and aripiprazole have been found effective, as monotherapy treatments, for prevention of manic episodes, and quetiapine has unpublished data suggesting it may prevent both manic and depressive episodes. It may soon present a challenge to lithium as the mood stabilizer with the best evidence base. This remains to be seen.

There is evidence that the SGAs olanzapine, quetiapine, ziprasidone, and aripiprazole, when added to lithium or valproate, can increase maintenance efficacy for the manic phase. In the case of quetiapine, the depressive phase was also helped.

16.4.2 Newer Anticonvulsants

Newer anticonvulsants such as topiramate, gabapentin, pregabalin, tiagabine, zonisamide and levetiracetam, which are generally thought to exert their therapeutic effects by enhancing GABA transmission, may also be effective for the treatment of bipolar disorder.(Johannessen and Landmark, 2008) However, when used, they should be considered to be adjunctive treatments only (e.g., to decrease concurrent anxiety); the evidence base is insufficient to recommend their use as primary agents for the treatment of mood disorder symptoms.(Anand, Bukhari et al. 2005; Grunze, Langosch et al. 2003; Grunze, Normann et al. 2001; Keck, Strawn et al. 2006; Macdonald and Young, 2002; Pande, Crockatt et al. 2000; Vieta, Goikolea et al. 2003; Vieta, Manuel Goikolea et al. 2006; Vieta, Sanchez-Moreno et al. 2003; Yatham, Kusumakar et al. 2002; Young, Geddes et al. 2006; Young, Geddes et al. 2006)

Further Notes on the Clinical Approach to Bipolar Patients

Mood stabilization is frequently difficult to achieve in bipolar disorder. Although the goal is to use as few medications as possible and rely on mood stabilizers whenever possible, it is common that more complex psychopharmacology regimens are required. The American Psychiatric Association's recently released updated Practice Guidelines for the Treatment of Bipolar Disorder contains a comprehensive review of the current knowledge base on the psychopharmacology of this disorder.(APA, 2009)

The Systematic Treatment Enhancement Program – Bipolar Disorder (STEP-BD) is a publically funded project designed to add to our understanding of how to best treat this disorder. The program enrolled 4,360 bipolar patients who are being followed longitudinally at 15 sites. Some of these patients agree to enter controlled studies of a variety of psychosocial and psychopharmacological interventions. Among the significant findings to date are the following:

- Psychotherapy is effective for bipolar depression but it is a slow process. It takes 169 days vs. 279 days in the control group.(Miklowitz, Otto et al. 2007)

- Antidepressants (bupropion, paroxetine) are not more effective than placebo for bipolar depression (24% for the antidepressants vs. 27% for the placebo in a 6-month trial). The antidepressants did not induce more switches to mania (10% vs. 11%), but the patients who participated in this study were probably at very low risk for switching.(Sachs, Nierenberg et al. 2007)
- Other STEP-BD data did show that use of antidepressants was associated with more manic symptoms.(Goldberg, Perlis et al. 2007)
- 262 suicide attempts and 8 completed suicides have occurred in this patient sample over a 6-year period. Lithium seemed to offer no protective effect, contrary to data from other studies strongly suggesting that lithium helps lower suicide risk in bipolar patients. However, the patient sample clearly had a very low risk of suicidal behaviors so it was not the best population to demonstrate lithium's possible benefit on this symptom.(Marangell, Dennehy et al. 2008)

Table 4 summarizes the characteristics of commonly used mood stabilizing medications.(Hyman, Arana et al. 1995; Rosenbaum, Arana et al. 2005; WHO, 2007; PDR, 2008; Stahl, 2005; Taylor, Paton et al. 2007)

TABLE 4. COMMONLY USED MOOD STABILIZING MEDICATIONS

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Lithium Carbonate (Lithobid®, Eskalith®)	Start: 300 mg po bid-tid and check serum trough level after 4-5 days (after steady state) then adjust as needed	Check baseline chemistries, kidney function, thyroid function (TSH), ECG (r/o sinus node dysfunction); once target dose is reached, check level, chemistries, kidney function, TSH, every 3-6 months initially, then every 6-12 months; NSAIDs, thiazide diuretics, ACE inhibitors, metronidazole, and tetracyclines can increase lithium level. On WHO Essential Medicines List for bipolar disorders.Mania/Maintenance in bipolar disorder

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Divalproex Sodium, Valproic Acid, Valproate (Depakote®, Depakote ER®, Depakene®)	Start: 250 mg po tid and check serum trough level after 4-5 days, then adjust as needed, can use loading dose of 20-30 mg/kg to hasten response	Check baseline LFTs and CBC; once target dose is reached check serum level, LFTs and CBC every 3-6 months initially then yearly; can inhibit the glucuronidation of lamotrigine; can inhibit CYP2C9, CYP2C19; aspirin can increase levels; valproate is highly protein-bound so will increase free warfarin levels. On WHO Essential Medicines List for bipolar disorders and as an anticonvulsant.Mania/Mixed episodes associated with bipolar disorder/Migraine prophylaxis/Specific seizure disorders (see package insert)
Carbamazepine (Tegretol®, Carbatrol®, Equetro®)	Start: 200 mg po bid then check serum trough level after 4-5 days. Dose requirements gradually increase over the first month due to cytochrome enzyme induction.	Check baseline CBC, sodium, LFTs; once target dose is reached check serum level, CBC and LFTs every 3-6 months initially, then yearly; induces CYP1A2, CYP2C9, CYP2C19, CYP3A4; itself is a CYP3A4 substrate. On WHO Essential Medicines List for bipolar disorders and as an anticonvulsant.Acute mania and mixed episodes /Trigeminal neuralgia/Specific seizure disorders (see package insert)

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Lamotrigine (Lamictal®)	Start: 25 mg po q am for first 2 weeks, then 50 mg po q am for 3rd and 4th week, then 100 mg po q am on 5th week, 200 mg po q am on 6th and 7th week, slower titration with concomitant valproate and faster titration and higher doses with concomitant carbamazepine	No laboratory monitoring necessary; valproate and sertraline can increase levels; monitor for rash and Stevens-Johnson Syndrome.Maintenance treatment for bipolar I disorder in patients treated for acute mood episodes with standard therapy/ Specific seizure disorders (see package insert)

- ® Generic and U.S. brand name(s).
- Dosing should be adjusted downwards ("start low, go slow" strategy) for the elderly and/or the medically compromised.
- Abbreviations: ACE-Angiotensin Converter Enzyme; bid-(bis in die) twice a day; CBC-Complete Blood Count; CYP-Cytochrome P450 enzyme; ECG-Electrocardiogram; kg-kilogram; LFT-Liver Function Tests; mg-milligram; NSAIDS-Non-steroidal Anti-inflammatory Drugs; tid-(ter in die) three times a day; TSH-Thyroid Stimulating Hormone; po-(per os) orally; WHO-World Health Organization.

16.5 Stimulants and Other ADHD Medicines

The use of psychotropics for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents is beyond the scope of this chapter. In adults, the diagnosis of ADHD is controversial but guidelines have been developed.(Gibbins and Weiss, 2007) Diagnosis of adult ADHD is predicated on plausible historical evidence of childhood onset.(APA, DSM, 2000) This is often difficult to establish retrospectively, and when earlier ADHD symptoms are suspected, it is difficult to rule out other etiologies for these symptoms (e.g., family stressors, childhood depression, learning disorders, etc.). Nevertheless, there are adults with undiagnosed ADHD, many of whom have other comorbid psychiatric illnesses, who continue to suffer chronic symptoms through adulthood and may benefit from treatment. Others may have had a clear history and diagnosis of ADHD in childhood and as adults may need to have pharmacological treatments considered or resumed.

16.5.1 Stimulants

Stimulants are the most effective and the first-line treatment for non-substance-abusing patients with ADHD. Amphetamine-like stimulants are sympathomimetic amines that likely enhance norepinephrine and dopaminergic transmission. They may disrupt the presynaptic storage of these transmitters and enhance their release—in both the ascending reticular activating system as well as in the regulation of "top-down" cortical-thalamic-striatal circuits.(Nestler, Hyman et al. 2009) Methylphenidate, dextroamphetamine and

amphetamine salts are examples of psychostimulants used in the treatment of ADHD. Assuming correct diagnosis and adequate dose, stimulants' beneficial effects on attentional symptoms, impulsivity and hyperactivity are immediate and subside with medication clearance. Short half-life formulations need to be administered multiple times during the day, but not near bedtime. Stimulant side effects include decreased appetite, insomnia, and anxiety, necessitating gradual dose titration to improve tolerability. Blood pressure and heart rate can also increase with stimulant administration so patients with cardiac disease may not be good candidates for treatment with stimulants. Possible growth retardation and the development of transient tics, although of concern in children, are not likely to be problematic in adults. Chronic stimulant use (or overdose) can lead to psychosis; in susceptible individuals, increased psychosis can be seen after just one dose.(Curran, Byrappa et al. 2004) Medication interactions of note include that stimulants should not be combined with MAOIs.

The major concern regarding the use of stimulants, however, is the risk of abuse and dependence. This seems related to the stimulants' ability to increase dopaminergic effects in the reward and reinforcement circuitry in the nucleus accumbens. Euphoria, tolerance, and addictive behaviors may develop in susceptible individuals. In the United States, therefore, amphetamine-like stimulants are highly regulated; they are "Schedule II drugs"-- which indicates that the Drug Enforcement Administration (DEA) designates them as being in the highest risk category for controlled substances that have an established therapeutic use. The risks of addiction and misuse have led some clinicians to be wary of using stimulants even when treatment with these medications is otherwise medically indicated. However, if the diagnosis of ADHD is accurate, these medications should not be avoided in patients who do not have a history of substance abuse. A clear risk and benefit assessment is necessary. Appropriate monitoring and supervision may decrease the risk of abuse. Recent data suggest no increase in risk of subsequent abuse of stimulants when children and adolescents with ADHD are treated with stimulants.(Biederman, Monuteaux et al. 2008) Notably, there was no decrease in risk either, i.e., no protective effect from treatment. This is controversial however as ADHD is considered to be a risk factor for substance abuse; other data regarding treatment of ADHD as a way to decrease the risk of substance abuse is mixed.(Wilens, 2004; Wilens, Faraone et al. 2003)

Stimulants have also been historically used in the treatment of anergic medically ill, mildly depressed, often elderly patients. Response can often be noted in a matter of days. There is no evidence however that these medications are effective antidepressants in other patients with major depression.(Satel and Nelson, 1989)

16.5.2 Non-Stimulant Medicines for ADHD

Atomoxetine is a norepinephrine and dopamine reuptake inhibitor (Bymaster, Katner et al. 2002) which has shown efficacy in, and has been primarily marketed for, the treatment of ADHD.(Michelson, Adler et al. 2003) As might be expected by its mechanism of action, it may also have antidepressant effects but there are no published data to support its use in the treatment of depression. Unlike stimulants which can rapidly improve ADHD symptoms, atomoxetine requires several weeks of treatment before response occurs. Response is generally less robust than with stimulants. Atomoxetine may cause increases in blood pressure, insomnia and possible weight loss. It is not associated with abuse or dependence.

In adults, other agents with noradrenergic and/or dopaminergic effects may be helpful in the treatment of ADHD symptoms, although again response is generally weaker than that expected from stimulants.(Meszaros, Czobor et al. 2007) These include bupropion (Wilens, Spencer et al. 2001), tricyclic antidepressants (especially the more noradrenergic desipramine and nortriptyline), (Higgins, 1999; Prince, Wilens et al. 2000; Wilens, Biederman et al. 1996) venlafaxine (Popper, 1997), modafinil (a wakefulness-promoting drug with unknown mechanism of action)(Biederman, Swanson et al. 2006) and clonidine.(Connor, Fletcher et al. 1999) SSRIs and antipsychotics are not effective in the treatment of ADHD.

Table 5 summarizes characteristics of selected ADHD medications.(Hyman, Arana et al. 1995; Rosenbaum, Arana et al. 2005; PDR, 2008; Stahl, 2005; Taylor, Paton et al. 2007) Antidepressants used in the treatment of ADHD are listed in Table 1.

TABLE 5. SELECTED ADHD MEDICATIONS

MEDICATION	DOSING	COMMENTS/FDA INDICATIONS
Methylphenidate (Ritalin®, Ritalin LA®, Ritalin SR®, Concerta®, Daytrana®, Metadate CD®, Metadate ER®, Methylin®) And Dexmethylphenidate (Focalin®, Focalin XR®)	For methylphenidate, Ritalin: Start: 5 mg po bid (morning and afternoon) and increase weekly by 10 mg/day, divide bid or tid with last dose not after 6 pm, maximum 60 mg/day with bid-tid dosing.	Carries risk of abuse; may decrease appetite and cause insomnia.Treatment of ADHD and narcolepsy
Amphetamine salts (Adderall®, Adderall XR®)	For Adderall: Start: 5 mg po q am and increase weekly by 5 mg/day, maximum 60 mg/day with bid dosing (morning and afternoon)	Carries risk of abuse; may decrease appetite and cause insomniaTreatment of ADHD and narcolepsy
Dextroamphetamine (Dexedrine®, Dextrostat®)	Start: 5 mg po q am and increase weekly by 10 mg/day, maximum 40 mg/day with bid dosing (morning and afternoon)	Carries risk of abuse; may decrease appetite and cause insomnia.Treatment of ADHD and narcolepsy
Atomoxetine (Strattera®)	Start: 40 mg po q am or divided bid (morning and afternoon), after 3 days increase to 80 mg/day, maximum 100 mg/day, reduced dosing with hepatic insufficiency	No risk of abuse; slower response than with stimulants; CYP2D6 substrate.Treatment of ADHD

- ® Generic and U.S. brand name(s).
- Dosing should be adjusted downwards ("start low, go slow" strategy) for the elderly and/or the medically compromised.

- Abbreviations: ADHD-Attention Deficit/Hyperactivity Disorder; bid-(bis in die) twice a day; CYP-Cytochrome P450 enzyme; mg-milligram; po-(per os) orally; tid-(ter in die) three times a day; q-(quaque) every.

16.6 Treatments for substance abuse/dependence

The past few decades have seen a dramatic increase in the number of pharmacological options available for the treatment of substance abuse disorders. Pharmacotherapeutic treatments are now available for the treatment of opioid dependence, alcohol dependence and nicotine dependence. Detailed algorithms for the use of pharmacotherapy in addiction disorders may be found at the website of the International Psychopharmacology Algorithm Project (www.ipap.org). The medical treatment of withdrawal states that emerge upon substance discontinuation are not covered in this chapter, but have been reviewed elsewhere.(Rosenbaum, Arana et al. 2005; Taylor, Paton et al. 2007) In treating patients with substance abuse, the beneficial effects of psychosocial interventions should not be overlooked.(Dutra, Stathopoulou et al. 2008)

16.6.1 Medications for Opioid Dependence

Methadone, a synthetic opioid mu-receptor agonist, is a long-acting analgesic that has shown efficacy in maintenance therapy for patients with a history of opioid dependence. Although methadone (at relatively low doses) can be prescribed as an analgesic by individual physicians in the United States, methadone for the treatment of heroin dependence can only be dispensed by centers registered and authorized to do so by regulatory agencies. The methadone dose is gradually increased over many months in patients attending these centers until a dose (of usually 90-120 mg/day or higher) is reached that stops cravings for illicit opiates and stops drug seeking behaviors.(Faggiano, Vigna-Taglianti et al. 2003) Methadone can cause respiratory depression (especially in patients who are not tolerant to opioids), additive CNS effects with concurrent use of other sedatives, QT prolongation(Ehret, Voide et al. 2006) and constipation. Levomethadylacetate (LAAM) is similar to methadone except with a longer half-life requiring less than daily administration, but it has been discontinued due to reports of it causing torsades de pointes arrhythmias.

Physicians should be aware that patients maintained on high dose methadone who are admitted to the medical/surgical wards of hospitals for unrelated medical care are likely to need to continue their daily dose of methadone. However, high doses should never be administered without independent confirmation with the methadone center administering this drug to confirm the actual dose that the patient has been receiving prior to admission. Even 3-4 days of methadone discontinuation may significantly reduce patients' tolerance to the respiratory effects of this drug. To decrease the risk of death from respiratory depression, a single dose of methadone should never exceed 20 mg when independent confirmation of higher doses is not possible. Subsequent dose increments can then be added as necessary and as tolerated.

Buprenorphine is an opioid mu-receptor partial agonist (with very high affinity for this receptor) that is used as an alternative to methadone for maintenance therapy in opioid

dependence.(Fudala, Bridge et al. 2003) In the United States it can be prescribed in an office-based setting (for example with weekly counseling and weekly dispensing)(Fiellin, Pantalon et al. 2006) without requiring daily administration in a methadone center. Buprenorphine is less dangerous than methadone in overdose with a lower risk of respiratory depression. Concurrent use of benzodiazepines or alcohol however significantly increases the risk of death from respiratory depression(Megarbane, Hreiche et al. 2006; Kintz 2001); therefore patients with a history of polysubstance abuse may not be good candidates for buprenorphine maintenance therapy. When used in outpatient treatment buprenorphine is combined with the opioid antagonist naloxone and administered sublingually. In sublingual form the buprenorphine is absorbed while the naloxone is not. When absorbed through the GI tract, naloxone undergoes extensive first-pass liver metabolism decreasing its systemic availability. Naloxone is added to discourage intravenous abuse of this medication: if this combination is misused intravenously, the naloxone effect predominates and blocks any opioid effect. Buprenorphine may also be beneficial in chronic pain patients who are at risk of opioid dependence; higher doses may be needed when buprenorphine is used as an analgesic.

16.6.2 Medications for Alcohol Dependence

Disulfiram, one of the earliest treatments developed for addictive disorders, acts by producing unpleasant physical effects if alcohol is concurrently consumed. It disrupts ethanol metabolism by irreversibly inhibiting aldehyde dehydrogenase, thereby leading to a significant accumulation of ethanol metabolite acetaldehyde which is associated with severely unpleasant adverse effects (and cardiac stress). Although there is no evidence that it helps maintain abstinence over the long run, it may be useful as a disincentive to ethanol use in the short term.(Suh, Pettinati et al. 2006) It retains its effect on aldehyde dehydrogenase for up to 2 weeks, so even if the patient stops taking disulfiram and plans to drink, there may be time to reconsider and enlist other supportive mechanisms to maintain sobriety before it loses effectiveness. Ultimately however, most patients who wish to drink do so by discontinuing disulfiram, and many drink while still on it, placing themselves at severe risk. Therefore, like all pharmacotherapies for ethanol dependence, external supports (such as family supervision of medication adherence) and nonpharmacological therapies (such as ongoing counseling and behavioral therapies) are needed for continued effectiveness.(Lingford-Hughes, Welch et al. 2004; Hughes and Cook, 1997) Notably, however, a recent randomized comparison of disulfiram, acamprosate and naltrexone (discussed below) in 243 patients, all of whom received brief cognitive-behavioral psychotherapy, showed disulfiram to be more advantageous than the other agents.(Laaksonen, Koski-Jannes et al. 2008)

Patients who are beginning disulfiram treatment should be informed of possible medication interactions and the need for avoidance of alcohol in foods (e.g., sauces) and topical preparations (e.g., perfumes). Disulfiram is not recommended for patients with cardiac disease, significant liver disease, peripheral neuropathy or psychosis.

Acamprosate may increase the number of abstinence days and decrease overall alcohol consumption long-term in alcohol dependent patients.(Boothby and Doering, 2005; Sass, Soyka et al. 1996; Whitworth, Fischer et al. 1996; Mann, Lehert et al. 2004; Kranzler and Van Kirk, 2001) Its mechanism of action is unclear although it is thought to involve the enhancement of GABA transmission and possibly the antagonism of the excitatory neurotransmitter glutamate.(Littleton and Zieglgansberger, 2003) It is generally well-tolerated,

with mild GI symptoms as the most commonly seen adverse effects. It is renally excreted and may be administered to patients with liver disease. Recent evidence from a large multicenter study, however, has shed doubt on the effectiveness of acamprosate (Anton, O'Malley et al. 2006)—see below.

Naltrexone is an opioid receptor antagonist. Alcohol can increase the release of endogenous opioids in the brain which may contribute to its euphoric effects. Naltrexone may reduce this opioid-mediated aspect of alcohol's reinforcing properties, and modestly reduce alcohol use in dependent patients.(Anton, 2008; Srisurapanont and Jarusuraisin, 2005) It appears to be most beneficial in severe alcoholics.(Pettinati, O'Brien et al. 2006) A long-acting (i.e., every 4 weeks) injectable preparation is also available.(Garbutt, Kranzler et al. 2005; O'Malley, Garbutt et al. 2007) Naltrexone may cause mild GI symptoms and an infrequent transaminitis that requires monitoring. Patients on naltrexone must not be given opiates for pain management: overdose and death can result from the high opiate doses needed to override the effect of naltrexone.

Some studies have suggested superior efficacy of naltrexone as compared to acamprosate.(Anton, O'Malley et al. 2006; Morley, Teesson et al. 2006; Rubio, Jimenez-Arriero et al. 2001) The recent U.S. government-sponsored COMBINE study which compared naltrexone vs. acamprosate vs. the combination of the two, all combined with medical management (i.e., brief meetings with a healthcare provider modeled on a primary care setting), found naltrexone to be more effective than acamprosate. It also found that the meetings with a healthcare provider increased the likelihood of abstinence.(Anton, O'Malley et al. 2006) It should be noted that the dose of naltrexone used was twice the usual maximum dose (100 mg/day vs. 50 mg/day). Individuals with a specific polymorphism of the mu-opioid receptor gene (OPRM1), i.e., individuals with an Asp40 allele—coding for a receptor with increased beta-endorphin binding and activity(Bond, LaForge et al. 1998)—may be more likely to respond to naltrexone.(Anton, Oroszi et al. 2008)

Off-label use of naltrexone may also be considered in opioid dependent patients—where higher doses are usually needed—if there are significant external supports and motivation to ensure adherence to this medication.(Kirchmayer, Davoli et al. 2003) Highly motivated addicted physicians and other professionals are examples of patients who may benefit from naltrexone treatment for opiate dependency.(Ling and Wesson, 1984; Washton, Gold et al. 1984)

16.6.3 Other Medications for Alcohol Dependence

There is recent evidence to support the use of the anticonvulsant topiramate for the treatment of alcohol dependence.(Johnson, Ait-Daoud et al. 2003; Johnson, Rosenthal et al. 2007) Ondansetron, an antiemetic with 5HT3 serotonin receptor antagonist activity, has also emerged as an agent with possible efficacy for this indication.(Johnson, Ait-Daoud et al. 2000; Johnson, Roache et al. 2000) The antidepressant mirtazapine is also a 5HT3 antagonist but has not been studied for this indication.

16.6.4 Medications for Nicotine Dependence

Nicotine replacement therapy is used to decrease withdrawal symptoms during smoking tapering and cessation and can double the odds of quitting.(Silagy, Lancaster et al. 2004) Nicotine replacement can be delivered transdermally via a patch, or by gum, oral inhaler, nasal spray or dissolving lozenge. All modes of delivery are likely to be effective(Silagy, Lancaster et al. 2004) Actual dosing and duration of treatment vary slightly for each formulation, although all nicotine replacement treatments involve setting a target date for smoking cessation followed by a gradual taper of the nicotine over 2-3 months. In a review of 88 trials, success rates on 6-12 month follow-up averaged 16% vs. 10% on placebo.(Silagy, Mant et al. 2000) Patients should therefore be encouraged to make repeated efforts to quit. Caution should be used in patients with a history of cardiac disease, especially when using the nicotine patch (avoid the patch if there is a history of serious arrhythmias, angina or immediately post-MI). Patients should not smoke at all while wearing the transdermal nicotine patch. Nausea and headaches can occur frequently with nicotine replacement therapy.

Bupropion, an antidepressant with possible dopaminergic effects (see section on antidepressants), is also efficacious for smoking cessation.(Jorenby, Leischow et al. 1999) Bupropion should be started two weeks before the target stop date and then continued for at least 3 months. The addition of nicotine replacement therapy to bupropion can increase the chances of abstinence compared to the use of either drug alone.(Jorenby, Leischow et al. 1999)

Varenicline is an alpha4beta2 nicotinic acetylcholine receptor partial agonist, with high affinity for this receptor. It is the latest advance in nicotine addiction treatment. It may have effectiveness that is comparable to, or greater than that of bupropion for smoking cessation.(Gonzales, Rennard et al. 2006; Jorenby, Hays et al. 2006; Tonstad, Tonnesen et al. 2006) Although varenicline appears to be generally well-tolerated, treatment-emergent mood changes and psychosis have been reported in susceptible patients.(Freedman, 2007; Kohen and Kremen, 2007) Because of its cost it is often restricted by pharmacy benefit managers to patients who have failed nicotine replacement and bupropion therapy.

Table 6 summarizes the characteristics of medications used for substance abuse/dependence disorders.(WHO, 2007; PDR, 2008; Hyman, Arana et al. 1995; Rosenbaum, Arana et al. 2005; Stahl, 2005; Taylor, Paton et al. 2007)

TABLE 6. MEDICATIONS FOR SUBSTANCE ABUSE/DEPENDENCE

MEDICATION	DOSING	COMMENTS/FDA INDICATION

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Methadone (Opioid analgesic) (Dolophine®, Methadose®)	Gradually increased over many months at specialized methadone maintenance centers only, to reach a dose that would stop cravings for illicit opiates-see text; analgesic doses are much lower	The use of prescribed opiates for addicts is controversial, but effective; not curative; requires attendance at a methadone clinic for daily administration; may increase QTc; CYP3A4 substrate. On WHO Essential Medicines List for substance dependence.Detoxification and temporary maintenance treatment of narcotic addiction/Relief of severe pain
Buprenorphine with and without naloxone (Partial opioid agonist with or without opioid antagonist) (Suboxone®, Subutex®)	Do not start until patient is experiencing moderate opiate withdrawal. Start: 4 mg sublingually bid-tid, usual maintenance dose is 16-20 mg/day or less, in divided doses	May be given as take home prescription by trained physicians; less regulated than methadone, and considerable street role and usage is occurring; CYP3A4 substrate.
Opioid dependence Acamprosate (GABA analog) (Campral®)	Start: 333 mg po tid and increase to 666 mg po tid after 2-3 days	Renally cleared; check baseline kidney function and adjust dose with decreased function; can continue even with alcohol relapse; concurrent naltrexone may increase serum levels; suicidality rates higher in acamprosate treated patients compared to placebo groups.Maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Disulfiram (Aldehyde Dehydrogenase Inhibitor) (Antabuse®)	Start 24 hours or longer after last alcohol use. Start: 125 mg po q am and increase after 4 days to 250 mg po q am and continue, maximum 500 mg/day	Check baseline LFTs before treatment and after 2 weeks and then every 3-6 months thereafter.Aid in the management of selected chronic alcoholics who want to remain sober and commit to supportive and psychotherapeutic treatment
Naltrexone (Opioid antagonist) (ReVia®, Vivitrol®)	For oral naltrexone, ReVia: Start: 25 mg po q am after meal then increase to 50 mg po q am after 3 days, do not start until free from opioids for 7-10 days	Check baseline LFTs, then monthly for 3 months, then every 3-6 months thereafter; available in long-acting IM form for every 4 weeks administration; give patient medi-alert card or bracelet.Treatment of alcohol dependence and to block effects of exogenously administered opioids
Bupropion (Antidepressant) (Zyban®, Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	For bupropion, Zyban, Wellbutrin: Start while still smoking. Start: 75-100 mg po bid (morning and afternoon) and increase after 4-7 days to 150 mg po bid, set cigarette cessation target date 2 weeks into treatment.	May be combined with nicotine replacement therapy; CYP2D6 inhibitor.Aid to smoking cessation treatment/MDD/Prevention of MDE in patients with seasonal affective disorder
Varenicline (Nicotine Acetylcholine Receptor Agonist) (Chantix®)	Start: 0.5 mg po bid for 7 days, then 1 mg po bid and continue for 12-24 weeks	Treatment-emergent neuropsychiatric symptoms and suicidality reported.Aid to smoking cessation treatment

MEDICATION	DOSING	COMMENTS/FDA INDICATION
Nicotine (Commit®, Nicoderm®, Nicorette®, Nicotrol Inhaler®, Nicotrol Nasal Spray®)	For Nicoderm patch: Stop smoking, then dosing depends on cigarette use: Ex.: If greater than 10 cigarettes/day then: 21 mg patch TD each day for 6 weeks, then 14 mg TD each day for 2 weeks then 7 mg TD each day for 2 weeks then stop, other dosing depends on formulation	Nicotine replacement therapy also serves to eliminate hydrocarbon toxicity and carbon monoxide inhalation associated with cigarette use.To reduce withdrawal symptoms associated with smoking cessation

- ® Generic and U.S. brand name(s).
- Dosing should be adjusted downwards ("start low, go slow" strategy) for the elderly and/or the medically compromised.
- Abbreviations: bid-(bis in die) twice a day; CYP-Cytochrome P450 enzyme; FDA-Food and Drug Administration; GABA-Gamma-Aminobutyric Acid; IM-intramuscular; LFT-Liver Function Tests; MDD-Major Depressive Disorder; MDE-Major Depressive Episode; mg-milligram; po-(per os) orally; q-(quaque) every; TD-transdermally; tid-(ter in die) three times a day; WHO-World Health Organization.

16.7 Conclusion

Over the last five decades, multiple medications have become available for the treatment of patients with psychiatric disorders. TCAs, MAOIs, SSRIs, SNRIs and others antidepressants have expanded current treatment options for depressive and anxiety disorders. Anxiolytics, including benzodiazepines and non-dependence-producing alternatives, are available for the treatment of severe anxiety disorders. First and second generation antipsychotics with different receptor profiles and side effect profiles have expanded the choices for patients with psychotic disorders. Lithium and other medications with mood stabilizing properties are available for use in patients with bipolar disorder. New formulations of stimulants and non-stimulant agents can be used in adults with attention-deficit/hyperactivity disorder. Finally, pharmacological therapies for the treatment of substance abuse and dependence disorders have been greatly expanded in recent years.

Medical students and physicians should become familiar with these medications and obtain some facility in using them. As always, the science and art of medicine comprise the ability to appropriately and carefully apply that which is learned in textbooks to a specific patient. In the clinical setting, pharmacotherapeutic treatments should be used judiciously: the risks and benefits of treatments should be considered so that every effort is made to "first do no harm." One should employ the strategy of using one medication at a time, so as to have the opportunity to know what is actually working and not working. The goal is to provide relief and lessen suffering, preferably in the most evidence-based and cost-effective manner possible. Finally, students and clinicians should keep in mind that for pharmacotherapeutic

interventions to be successful there must also be appropriate psychosocial support and treatment. Only then can safe, effective, and comprehensive treatment be provided.

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17 Electroconvulsive Therapy and Transcranial Magnetic Stimulation

Neurostimulation or brain stimulation techniques have been used for many years with the hope that they can help alleviating symptoms of mental disorders. Generally, neurostimulation techniques can be defined as using a variety of different methods of stimulating the brain. In the past, there have been a variety of methods used, which are no longer used such as Cardiazol Shock Therapy, Insulin Coma Therapy, etc. Sometimes these treatment methods are referred to as biological treatment, as opposed to psychological treatment (psychotherapy) or pharmacological therapy (psychopharmacological agents).

In this chapter, we will look in more detail at Electroconvulsive Therapy and Transcranial Magnetic Stimulation.

17.1 Electroconvulsive Therapy

Electroconvulsive Therapy (ECT) is a well-established treatment method for psychiatric disorders. A convulsion (seizure) is induced by the application of electrical current to the brain by using 2 electrodes. The position of the electrodes is important and the most commonly used positions currently are (1) bilateral position, where the electrodes are placed symmetrically on both sides of the head. It can further be subdivided to (a) bitemporal placement when the 2 electrodes are positioned on both temporal areas and (b) bifrontal positioning where the electrodes are positioned on the forehead. (2) The electrodes can also be positioned only on the one side of the skull, thus stimulating only 1 hemisphere of the brain. Usually this is the right side and hence right unilateral (RUL) position.

17.1.1 Stimulus parameters

In the past, current with sine wave was widely used. More recently in the last 20-30 years, this has been modified to monophase brief pulse electrical current.

There are several parameters of the electrical stimulus, which are important. Current is measured in ampers and the most commonly used range is between 500 to 800 milliampers. Frequency of the brief pulse is typically anywhere between 20 to 120 Hz (pulse/sec). Individual pulse width varies usually between 0.25 to 2 msec. The duration of the stimulus is usually between 0.25 to 8 seconds or more. The total charge of electricity delivered at one stimulation is measured in coulombs and it is derived by the combination of different stimulus parameters. Most ECT machines can deliver a charge up to 1,000 millicoulombs or more, although the machines sold in the USA and Canada are usually limited to below 600 millicoulombs. The actual energy delivered depends on the charge and impedance; it is measured in jolts.

Another important parameter is the so-called seizure threshold. Seizure threshold is defined as the minimal charge (combination of individual parameters) able to produce a seizure. Once the threshold is established, the actual stimulus can be delivered at low dose (at seizure threshold), moderate dose (1.5 times seizure threshold), high dose (2 times seizure threshold) or even at suprathreshold (5 to 6 times seizure threshold).

17.1.2 Muscle Relaxation and General Anaesthesia

In order to reduce the possible traumas and injuries from the convulsion (seizure), a muscle relaxant medication has been widely used in order to partially paralyse the large muscles in the body. As this paralysis may be associated with significant fear and an anxiety response, the use of short acting general anaesthesia has been incorporated into the treatments.

17.1.3 Frequency of Treatments and Number of Treatment Sessions

The usual number of treatments per week is 2 to 3 and there does not appear to be any significant difference between the two schedules. There might have been suggestion that treatments delivered 3 times per week may be associated with faster response, but with more side effects, and this could be used by individual practitioners in order to make determination of the actual frequency. Treatments delivered every day and even more than 1 treatment per day are virtually no longer used. If there are significant cognitive side effects, some practitioners would reduce the frequency down to 1 treatment a week.

The total number of treatments varies widely but is generally regarded that a course of treatment is usually between 6 and 12 or more treatment.

17.1.4 Efficacy

In the past, response rates of 80% or higher have been reported in treatment of naive patients.

In direct comparisons with older antidepressant medication, ECT has consistently delivered better response rates. There is lack of evidence comparing ECT directly with newer antidepressant medications such as SSRIs or SSNRIs and others.

The efficacy of ECT is strongly related to its' stimulation parameters and there is consistent evidence for that. Bitemporal placement is generally regarded as more effective than unilateral, but seems to be associated with more cognitive side effects. More recently, there has been some evidence that right unilateral placement at suprathreshold stimulus dose is at least as effective as bilateral stimulation but is associated with fewer side effects. Meta-analysis suggests that bitemporal ECT associated with greater acute cognitive side effects compared to right unilateral ECT. Bifrontal placement of the electrodes has been less frequently evaluated. There are some reports suggesting that bifrontal placement of electrodes is as effective as bitemporal or right unilateral but is associated also with less cognitive side effects. It also appears that shorter pulse width and/or lower pulse frequency may have also lower seizure thresholds.

17.1.5 Indications for Use

ECT is currently used in the treatment of Major Depressive Disorder, Mania, Schizophrenia and Catatonia.

Use in Major Depressive Episodes/Disorders

Considerations for ECT as a first choice treatment for Major Depressive Episodes or Disorder are usually after a serious suicidal attempt or a very strong acute suicidal ideation. It can be considered also with severe depression with psychotic features in rapidity deteriorating physical status due to refusal of food and fluids. Sometimes patients who have responded well to previous ECT treatments would request that ECT is used as first choice and this should be taken into consideration as well.

The main use for ECT in Major Depressive Disorder is for treatment resistant depression after a lack of response to other treatment methods. It has been also well established that ECT is a safe and effective for treatment of depression during pregnancy.

Use of ECT in Other Conditions

ECT has been used in treatment resistant Mania. It could be used in Schizophrenia, which is resistant to Clozapine, and also in acute Catatonia. There have been case reports in the treatment of other conditions as well.

Contraindications for ECT Treatment

There are relatively very few absolute contraindications for ECT treatment and these are associated with increased intracranial pressure and space occupying lesion. Recent cardiovascular event is also a relative contraindication. A consultation with an internal specialist and/or anesthesiologist may be required in such cases.

17.1.6 Side Effects

ECT is a safe procedure with very low mortality rate calculated as 0.2 per 100,000 treatments approximating the risk of general anesthesia. The side effects are short term and include nausea, headaches, muscle pain, dental injuries and oral lacerations and myalgia. They seem to be short lived and respond to symptomatic treatment.

Of much more concern are the cognitive side effects and transient confusion has been reported. Anterograde and retrograde amnesia, word finding difficulties and deficits in memory may continue for longer periods of time. It seems that reducing the frequency of treatment from 3 to 2 times per week, the use of brief pulse rather than sine wave ECT machines, right unilateral or bifrontal positions of the electrodes instead of bitemporal and lower dose stimuli might reduce the frequency and intensity of cognitive side effects.

Allegations that ECT may cause brain damage have been consistently refuted. In fact, it seems that ECT may stimulate an increased production of neurotrophic growth factors

such as brain derived neurotrophic factor (BDNF) causing migration and proliferation of progenitor cells and growth of new neurons in the hippocampus. These findings are consistent with evidence of similar effects of various other antidepressant treatments and may be the final common pathway of the antidepressant effects.

ECT has a very negative perception by the general population, due in part of its portrayal in works of art, e.g., Oscar Winning "One Flew Over the Cuckoo's Nest."

17.2 Repetitive Transcranial Magnetic Stimulation

17.2.1 Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) is a newer stimulation technique used for research and in clinical practice in the last 10 to 15 years. It involves the application of strong magnetic field, which penetrates through the skull (hence transcranial) and superficially the brain, producing some local electrical current. These electric currents affect the functioning of neurons. The magnetic fields are the magnitude of 1.5 to 2.5 TESLA and are generated when electrical current is passed through a coil (electromagnetic induction).

The coils currently used for rTMS are usually of 2 types, round and figure 8 (butterfly) shaped. The figure 8 coils seem to be able to produce a stronger and more focal magnetic field compared to the round coil and is becoming more widely used. The stimuli delivered are repetitive and fall into 2 types: (1) low frequency rTMS, which is usually regarded for stimuli at or below 5 Hz. The lower frequency stimuli appear to produce transient reduction in cortical excitability at the area stimulated. (2) High frequency rTMS is a TMS at 5 Hz or more, usually 10 to 20 Hz. The high frequency TMS seems to increase the neuronal excitability at the area stimulated.

The actual stimuli are delivered in trains, which last several seconds, followed by inter-train intervals. Many consecutive trains can be delivered at each session. Sessions are delivered usually daily to 5 sessions per week. Earlier reports of rTMS evaluated the effects of 10 sessions (given over 2 weeks), but more recent trials have been between 4 and 6 weeks in duration. There are some further variations of the frequency sessions and sometimes they can be delivered in 2 sessions per day or 1 session every 2nd or every 3rd day. At the beginning of each treatment, the motor threshold is established. The motor threshold is defined as the minimal intensity of the stimulus able to produce muscle twitches in the contralateral abductor policis brevis. Subsequently, the intensity is set usually between 90 and 120% of this threshold.

Target areas to be stimulated are most commonly left or right dorsolateral prefrontal cortex (DLPFC). The use of rTMS has been mainly studied in the treatment of depression and the most evidence is for treatment of the left or right dorsolateral prefrontal cortex. The most evidence of successful treatment in depression is established to be occurring with stimuli with high frequency, rTMS on the left dorsolateral prefrontal cortex, although studies with low frequency right dorsolateral prefrontal cortex and different combinations of the two have also been studied.

Unlike ECT, the delivery of rTMS does not produce seizures and the patient remains alert through the treatment. There is no need of anaesthesia or any other additional interventions.

rTMS seems to have a more positive view from the lay public compared with ECT. There is also evidence that rTMS is producing much less cognitive side effects than ECT, if any.

17.2.2 Efficacy

There has been some controversy about the efficacy of rTMS in Depression where it has been mostly studied. Since the first case report in 1993, there have been many open label and randomized double blind controlled trials evaluating the effect of rTMS for treatment of Depression. A direct comparison of separate studies is difficult because of great variability of the stimuli parameters used and also of various methodologies. Earlier meta-analyses were not very convincing, but most recently with accumulation of more and larger studies, it has been shown that rTMS is an efficacious and safe, well tolerated treatment for depression.

rTMS has been used for treatment resistant Depression and a recent meta-analysis has found that both response and remission rates are significantly better in the active treatment group compared with placebo, although they have been usually lower than other methods for treatment resistant depression. Interestingly, it seems that the more recent studies are able to find higher response and remission rates in general. This could be explained by the improvement and the precision of site administering of the stimulus and the increase of the number of treatment sessions.

There is limited information about direct ECT vs. rTMS comparisons, but the existing data seems to show some superiority of ECT, unfortunately at the price of higher frequency of cognitive side effects.

Like ECT, rTMS has been shown to be followed by a high percentage of relapse after the acute treatment. In many centres, some form of continuation and/or maintenance rTMS has been occasionally offered, but there is no systematic evaluation of these approaches.

As mentioned above, the rTMS has been studied mainly in patients with Depression in either Major Depressive Disorder or Bipolar Disorder. It appears as though the patients who had a more severe disorder may be better candidates for treatment with rTMS but, at the same time a higher level of previous treatment resistance is a negative predictor of future response. A variety of studies have shown also some good response of patients who suffer from Depression co-morbid with Parkinson's Disorder, pain conditions and vascular Depression and also late-life Depression.

17.2.3 Side Effects and Tolerability

rTMS seems to be well tolerated and there have not been that many side effects reported. The most common side effect is pain in the site of stimulation, headaches, which usually respond easily to conventional symptomatic treatments. Concerns about hearing loss due to the loud clicking noise produced by the machine have been addressed through use of earplugs with 30 decibels protection during the treatment, by both patients and treating staff.

There have been a dozen case reports of seizures occurring during rTMS so far worldwide. Many of these seizures are due to underlying neurological conditions. With good screening and restriction of the intensity of the rTMS stimuli, this can be largely avoided.

17.2.4 Contraindications

Absolute contraindications include the presence of aneurysm clips, cranial implants, brain stimulators or electrodes or any other devices made of ferromagnetic material in the head with the exception of the mouth. Increased intracranial pressure, epilepsy, severe cardiovascular disease and other medical conditions are also contraindicated. Cardiac pacemakers are also an absolute contraindication. As there is no data of the effects of strong magnetic field on the fetus, rTMS is contraindicated in pregnancy.

In conclusion, both ECT and rTMS are useful addition to the treatment armamentarium for depression and other conditions.

18 Psychotherapy for Medical Students

The word psychotherapy comes from ancient Greek words psychē, meaning spirit or soul, and therapeia, to nurse or cure. Today, psychotherapy is a general term that refers to any of a range of techniques in which an intentional interpersonal dialogue is used to treat psychological distress or problems in living. Although some forms of psychotherapy are conducted in group settings, it is typically delivered in one-to-one sessions with a mental health provider. Provision of psychotherapy was initially restricted to psychiatrists but has evolved to now include diverse practitioners including psychologists, social workers, nurses, and counselors. Psychotherapeutic techniques are quite diverse but all are built around an experiential relationship through dialogue meant to enhance individual adaptation via healthier modes of communication and behavioral responses.

Over the years, psychotherapy and psychopharmacology have emerged as standard interventions to help patients overcome psychiatric illnesses. These treatment approaches can be used individually or in combination. Currently, substantial evidence confirms the efficacy of many psychotherapeutic modalities. Evidence is especially clear for time-limited therapies in the management of anxiety and mood disorders and also in promotion of health and sense of well-being in patients with schizophrenia, bipolar disorder, and chronic medical problems. Therapeutic alliance and the skill of the therapist are the most important factors determining the outcome of any form of psychotherapy.

This chapter provides the medical student with a brief overview of key forms of psychotherapy. Given that a substantial literature in the field has accumulated over decades of research, this review provides only an overview of the therapeutic techniques. This chapter offers brief descriptions of the following subtypes of psychotherapy:

- Psychodynamic therapy
- Brief psychodynamic therapy
- Behavioral therapy
- Cognitive behavioral therapy
- Interpersonal therapy
- Dialectical behavior therapy
- Family therapy
- Couples therapy
- Supportive therapy
- Group therapy

18.1 Psychodynamic Therapy (PDT)

Psychodynamic therapy defined the practice of psychiatry in the first half of twentieth century. It evolved mainly from Sigmund Freud's psychoanalytical principles, with significant

contributions from Anna Freud, Karl Jung, and Melanie Klein, among many others. The basic emphasis is on how early childhood experiences are vital in molding and establishing the psychological mechanisms which predominantly drive the unconscious. The aim of psychodynamic therapy is to identify, bring to notice, and reprocess repressed conflicts from previous experiences which are being unconsciously enacted in current interpersonal interactions leading to maladaptive patterns of behavior. PDT works best for mild to moderate problems in adjustment, as well as for depressive, anxiety, and personality disorders (1). Characteristics of patients who often do well with this form of therapy include those with psychological mindedness, motivation to get better, and the ability to trust and collaborate with therapists.

PDT can be long-term (1-5 sessions/week for a number of years), intermittent, or brief (<6 months in duration or 6-40 sessions in total). Irrespective of the duration, this form of therapy begins with a comprehensive assessment which lasts between 1-4 sessions. Apart from history taking, this phase involves explaining the process of therapy to the patient, and evaluating whether the patient has the ego-strength and is suitable to undergo PDT. Initial elements of transference and counter-transference (which are described soon herein) also may begin to emerge. Follow up sessions usually take place at a particular time every week. Therapeutic alliance is one of the most important factors determining the outcome of PDT.

Exploration of the unconscious drive is done by free association and dream analysis. In free association, the patient is encouraged to speak whatever comes to his mind without inhibition or censorship. The therapist uses "active listening" and looks for patterns or references relating to current interpersonal and developmental conflicts which can help understand the unconscious process. Freud's critical work on dreams has led to the use of dream analysis in understanding the unconscious. Freud called dreams as "the royal road to the unconscious." He described dream work as the process by which a latent dream is converted to a manifest dream by symbolization, displacement and condensation. In dream analysis, the therapist tries to reverse this process and thereby, identify the latent components, which in turn, reveal the unconscious desire.

During the course of psychodynamic therapy, the processes of transference, counter-transference and resistance repeatedly occur which may indicate or lead to the underlying unconscious conflicts or desires. The therapist must be aware of and assess these phenomena in therapy. Transference is an emotion experienced by a patient towards the therapist which is based on experiences from previous relationships. Counter-transference is the emotion evoked in therapist towards the patient which is determined by his or her past experiences. The therapist's efforts to understand transference helps in understanding how the past is continually re-enacted in present. Counter-transference is important to recognize as it might interfere with therapy.

Resistance is the unconscious blocking of the therapeutic process. It can manifest in a number of ways such as showing up late for appointments, staying silent during sessions and avoiding talking about core issues. Defense mechanisms constitute the executive function of the ego and help reduce anxiety. They can be healthy or pathological. Key defenses include denial, projection, splitting, projective identification, undoing, isolation of affect, intellectualization, introjection, and repression. Suppression, sublimation and humor are identified as mature defense mechanisms.

Therapists work with patients to identify and deal with transference, resistance, and defense mechanisms. Several strategies are used to achieve this such as making an observation, interpretation, clarification and validation. Therapy eventually guides the patient in reprocessing previous conflicts which, in turn, helps break the maladaptive behavior patterns of the present. As the goals of therapy are realized and the patient has consolidated the tools learnt to overcome conflicts and maladaptive behaviors, the termination phase of therapy begins, with the therapist setting a date to end sessions.

It is important for therapists to have their own therapy to understand their own contribution to the therapeutic process. Good supervision and peer support are also vital tools.

Principles of psychodynamic therapy have revolutionized physician-patient interactions in all specialties. Even though in some respects it has fallen out of favor recently in comparison to briefer therapies, PDT still holds a unique position in psychotherapy and to a great extent underlies all the psychotherapies currently available. Longer term outcome studies reveal that psychodynamic therapies may yield profound and permanent personality maturation.

18.2 Brief Psychodynamic Therapy (BPT)

Alexander and French listed the benefits of time limited therapy using psychodynamic principles. In this era of emphasis on optimal resource utilization and cost-benefit analysis for interventions brief therapies have regained popularity. Such brief therapies may emphasize issues to do with cognitive, behavioral or psychodynamic (2). Similar to long-term psychodynamic therapy, BPT aims to identify and reprocess repressed conflicts from previous experiences which are being unconsciously enacted in the current interpersonal interactions and thus causing maladaptive patterns of behavior. However, BPT differs from long-term psychodynamic therapy in several aspects.

The usual number of sessions in BPT varies from 12-40 and is usually completed in six months, following an initial comprehensive assessment that establishes a therapeutic alliance and identifies the major problem area (3). Using this as a template for future sessions, developmental conflicts, defense mechanisms, transference, counter-transference, and resistance are identified and reprocessed to promote a corrective emotional experience in therapy. Given a shorter duration of therapy, the therapist has a more active role compared to long-term psychodynamic therapy, which involves a substantial reliance on limited but sometimes pivotal interpretations. In BPT, the therapist uses challenge, confrontation, and anxiety-provoking techniques while guiding the patient towards conflict resolution (4). Considering such an active and often anxiety- provoking therapeutic work to achieve outcomes, it is important that patients in BPT are able to trust and work with the therapist and also can openly acknowledge emotional distress from an interpersonal viewpoint (5).

Several types of BPT have evolved based on drive, relational, and integrative (using both drive and relational) models. Examples include:

- Brief focal psychotherapy (Tavistock-Malan): This involves an average of 20 sessions focused on internal conflicts present since childhood and processing of transference reactions. The termination date is determined after a few sessions.
- Time limited psychotherapy (Boston University-Mann): This usually consists of 12 sessions focused on resolution of the chronic distress due to negative self-image.

- Short-term dynamic psychotherapy (McGill University-Davanloo): This entails a flexible approach over 5-25 sessions aimed at resolution of oedipal conflict.
- Short-term anxiety provoking psychotherapy (Harvard University-Sifneos): This aims to resolve oedipal conflict via anxiety-provoking questions and confrontation.

Clinical applications: BPT has been shown to be effective for a variety of anxiety disorders including panic disorder, phobias, generalized anxiety disorder (GAD), and post traumatic stress disorder (PTSD). Patients with depressive and eating disorders of mild-moderate severity also benefit from this therapeutic approach. Well-designed research studies are needed in the future to assess its long-term efficacy (6).

18.3 Behavioral Therapy

Behavioral Therapy (BT) utilizes techniques derived from both Pavlov's classical and Skinner's operant conditioning. BT identifies maladaptive behaviors as the source of psychological distress and attempts to improve quality of life by altering and modifying these. BT works best for specific behavioral symptoms such as phobias and compulsions.

Several subtypes of BT have been developed for use either alone or in combination with pharmacotherapy or cognitive therapy for treatment of a variety of psychiatric disorders:

a) Systemic desensitization: This technique, initially developed by Wolpe, is particularly helpful for phobic disorders with a clearly identifiable precipitating factor. In the initial phases, relaxation techniques including deep breathing and progressive muscle relaxation are taught and practiced. A hierarchy of anxiety-provoking stimuli is constructed with the help of the patient. For example, a person afraid of using an elevator would go through therapeutic steps of first imagining standing in front or riding the elevator, then on to seeing pictures of elevator, then going to a building with an elevator, standing in front of the elevator, and eventually taking the elevator. Therapy moves from the least anxiety-provoking stimulus to highest (7). The patient is first exposed to the least anxiety- provoking stimulus and then encouraged to use the relaxation techniques till the anxiety decreases. This phenomenon, called reciprocal inhibition, continues until the patient is habituated and no longer feels anxious in response to that particular stimulus. Once this is achieved, therapy will progress along the hierarchy to the next stimulus. This process is repeated until the patient is ready to move to the next step on the hierarchy.

b) Flooding/Implosion: This is based on the concept that escape or avoidance of an anxiety-causing situation (phobia) maintains the fear. Patients are exposed to anxiety-provoking stimulus (not graded exposure) either in vivo (flooding) or imaginary (implosion) and not allowed to leave till their anxiety subsides (habituation). Compared to systemic desensitization, flooding leads to severe anxiety initially and may not be tolerated very well by some patients.

c) Aversion therapy: This is based on a "punishment model" and used to treat substance abuse disorders and paraphilias. A maladaptive behavior is combined with aversive (noxious) stimulus to decrease the repetition of maladaptive behavior. An example of this is an individual with alcohol dependence is given disulfiram. The next time this individual drinks alcohol, he will experience adverse effects such as nausea, vomiting, flushing and headache.

Similar techniques have been used to treat paraphilias. Though aversive conditioning may be effective initially, there is skepticism about compliance and long term benefits.

d) Exposure and response prevention: This is a key technique to treat Obsessive Compulsive Disorder (OCD) (8). Patients are trained to refrain from performing rituals (compulsions) despite having increased anxiety stemming from obsessional thoughts, images or impulses (response prevention). For example, a patient whose obsessions involve fear of contamination is asked to touch various surfaces (exposure) but refrain from washing hands (response prevention). Over time, this helps to break the vicious cycle of compulsive acts in response to obsessions.

e) Token economy: This is commonly used in settings where children, adolescents, and patients with mental retardation are treated. Desired adaptive behaviors are reinforced with tokens such as stars or tickets. Tokens are accumulated and exchanged at the end of a specified time period for gifts such as snacks, toys, watching television, or playing video games. When maladaptive behaviors occur then there is a penalty with a certain number of tokens is taken away. What makes a behavior desired or maladaptive and the rewards/penalty associated with them are clearly communicated in advance to the patients. Hence this technique promotes acquisition of good behaviors and autonomy.

f) Modeling: A patient initially observes a peer or a therapist perform a desired behavior that is positively reinforced. This is followed by the patient imitating the behavior to also get rewarded for this enactment. This leads to learning adaptive behaviors. Modelling is also referred to as social learning.

g) Shaping: This involves gradual change from a learned response to a desired one. Shaping is brought about by positive reinforcement of successive approximations of desired behavior.

h) Cognitive behavioral therapy (CBT): In CBT, behavioral techniques are used as an adjunct to cognitive strategies that reinforce learning. Examples include activity scheduling, graded task assignment, relaxation exercises, assertiveness training, thought record, coping cards, and biofeedback. Details of CBT are listed in the next section.

18.4 Cognitive Behavioral Therapy

Cognitive Behavioral therapy (CBT) was initially developed by Aaron T Beck for treatment of depressive disorders (9). Since then, CBT has gained widespread acceptance for managing anxiety disorders and has also been tailored to help patients with bipolar disorder, eating disorders, personality disorders, substance abuse disorders, and even psychotic disorders. CBT is a short term therapy with emphasis on collaborative relationship between therapist and patient.

Theoretical background: Information processing utilizes cognitive representations also termed as core beliefs or schemas. These schemas and the resulting automatic thoughts influence emotions and behavior and help deal with a great number of stimuli that we are constantly being exposed to (10). Multiple factors at the biological, developmental, social levels contribute to the formation of schemas.

Psychiatric disorders are characterized by dysfunctional schemae and maladaptive thoughts (cognitive distortions) that lead to abnormal affect and maladaptive behavioral patterns that

reinforce core beliefs. Examples of dysfunctional core beliefs include Beck's cognitive triad of pervasive negativity towards self, world, and the future as well as excessive fear of physical or psychological danger in anxiety disorders (11). Commonly seen cognitive distortions include over-generalizing, selective abstraction, minimization/ magnification, catastrophizing, and dichotomous thinking. CBT aims to empower patients with the ability to become aware of and change these maladaptive core beliefs and cognitive distortions.

CBT does not claim this model is the causal factor of psychopathology and reiterates the importance of taking into account multiple etiological factors including biological, social stressors. The usefulness of pharmacotherapy in helping patients is also noted (13).

Outline of CBT Sessions: The total number of hourly sessions varies from 5-20, with an average number being 12-16. Patients with residual symptoms or recurrent illness may find "booster" sessions helpful to maintain response (14). The first few sessions are aimed at getting comprehensive history and identifying current problems. Based on the problems, an attempt is made to elicit, test, and modify maladaptive schemae and cognitive distortions. Formal joint agenda setting, homework, and feedback are important tools to reinforce learning, maintain focus, and move in the right direction. Socratic questioning, emotional state during sessions (15), imagery, and role play are useful in uncovering and dealing with cognitive distortions. Generation of alternatives, examining evidence, decatastrophizing, reattribution, thought recording, and cognitive rehearsal are some of the techniques used to modify schemae/cognitive distortions (16).

18.4.1 Thought Record

Event

What happened? What were you doing? Who was involved? Automatic thought

Note down the most important thoughts/images which troubled you during that time.

Emotion

Which feelings or emotions (sadness, anxiety, anger etc)

Did you feel in that situation?

Adaptive answer

What is the evidence for the automatic thought? Are there any alternative explanations for the event? Result

Asses how much do you believe now in your automatic thoughts (0-100%) and in the intensity of your emotions (0-100%)

Adapted from `http://www.scielo.br/img/revistas/rbp/v30s2/en_a02tab04.gif`

Clinical Applications: There is significant research supporting efficacy of CBT in depressive and anxiety disorders (17). CBT has also been shown to be effective for dysthymia and in combination with medications for major depressive disorder, panic disorder, OCD, and generalized anxiety disorder. CBT principles have been used for modifying overvalued ideas seen in eating disorder and for symptom recognition, relapse prevention, and medication adherence in psychotic illnesses and bipolar disorder.

18.5 Interpersonal Therapy

Interpersonal psychotherapy (IPT) is a brief, time-limited therapy developed in the 1970s for the treatment of depression. This approach is based on the premise that depression is often closely intertwined with the patient's interpersonal relationships. The goals of IPT include reduction in symptoms and enhancement of communication skills in significant relationships. IPT is thus unique in its focus on improving patient interpersonal relations and social functioning and, thereby, improving depressive symptoms. Over the years, IPT has gradually evolved to become one of the foremost treatment modalities for depression, apart from pharmacotherapy and cognitive behavioral therapy (CBT). IPT assumes the development and maintenance of depressive symptoms occurs in a social and interpersonal context and, further, that the onset, response to treatment, and outcomes are influenced by interpersonal relations between the patient and significant others.

Historically, Harry Stack Sullivan's interpersonal theory of emotions formed the basis of interpersonal therapy. Over the years, Klerman and Weissman became leading exponents of and researchers in the field. Techniques utilized by these authors focus on the goals of 1) changing communication, and 2) solving interpersonal problems to help improve interpersonal relationships to improve emotional well-being. In contrast to CBT, IPT focuses on changing relationship patterns (not on distortions in cognitions); furthermore, there is minimal focus on systematized homework assignments in IPT. Typically, IPT is time-limited and usually once-a-week, for 12 to 20 sessions. The approach taken by most IPT therapists is to identify one or two problem areas and correlate the interpersonal aspects of these issues with symptom formation and maintenance. IPT can be divided into three phases: the initial phase, the middle phase and the termination phase.

Initial Phase: This is focused on a confirmation of the diagnosis of depression and education about depressive symptoms. This is followed by understanding significant interpersonal relationships and, thereafter, identifying target problem areas. After confirming the suitability for IPT, the therapist introduces principles of IPT to the patient, conducts an interpersonal inventory, and establishes a working formulation in the interpersonal context. The patient is assigned a limited sick role' to provide relief from performing the social role. The interpersonal formulation is based on one of four key interpersonal problem areas: grief, interpersonal deficits, interpersonal role disputes, or role transitions.

Middle Phase: This largely involves therapy "work." The therapist works with the patient to implement specific strategies related to one of the four problem areas. Furthermore, the therapist highlights how changes in patient interpersonal relationships relate to changes in symptomatology.

Termination Phase: Here the therapist discusses termination and encourages patients to understand and describe specific changes in their psychiatric symptoms, especially as they relate to improvements in the identified problem area. The therapist also assists the patient in consolidating gains, and helping him identify early warning signs of symptom recurrence.

18.6 Dialectical Behavior Therapy (DBT)

DBT evolved mainly from Marsha Linehan's efforts to decrease chronic suicidal/self-injurious behavior in patients with borderline personality disorder (BPD) (18). DBT uses a combination of cognitive, behavioral, and supportive strategies along with acceptance and mindfulness principles. It aims at enhancing and expanding patient motivation as well as their capability to reduce dysfunctional behavior.

Theoretical background: Emotional vulnerability is dependent on biological factors such as temperament and impulse dyscontrol. In the presence of an invalidating environment (such as parental/caretaker neglect or abuse), emotional dysregulation may emerge which constitutes the core problem (19). In response to stress, these patients engage in maladaptive behaviors such as suicidal, self-injurious, or avoidance to escape from distressing emotions (20). Such a pattern is often reinforced and learned. DBT uses problem solving, validation, and dialectics to break this cycle and develop healthier ways to manage stress.

Initially while problem solving, behavioral analysis is used to identify the sequence of internal events (emotional state), external events (stimulus), and consequences associated with problem behavior. Several strategies such as cognitive modification, behavioral skills training, solution analysis, didactic approach, and insight development are used to break the maladaptive cycle. Validation is a process of non-judgmental, active listening with communication of acceptance of patient's experiences.

Dialectical strategies underlie all the principles used in DBT and promote acceptance and change, flexibility with stability, and nurturing with challenging, to help patients overcome their limitations.

Outline of DBT Sessions: In the pretreatment stage, orientation is provided and informed consent and commitment to the program are obtained. The initial duration of ongoing DBT is usually one year (21). Priority is given to replace risky behaviors such as suicidal or self injurious behaviors with healthy alternatives.

DBT is delivered in four different settings: individual therapy, group skills training, telephone consultation, and therapist consultation. Patients individually meet for one hour every week with their primary therapist and review their treatment goals. This therapist is responsible for coordination of care across all the modes.

Group skills training uses a didactic approach and empowers patients with skills such as:

- Mindfulness to increase awareness and be in the present moment
- Emotional regulation to understand and accept emotions and thereby, reduce emotional vulnerability.
- Interpersonal communication skills
- Self-management to promote realistic goal setting, dealing effectively with environmental factors and relapse prevention

An individual therapist is available for telephone consultation at all times for crisis intervention. If the primary therapist is not available, coverage is arranged. Furthermore, therapists meet once a week for consultation, peer supervision, and feedback about using DBT effectively.

Clinical Applications: Most of the DBT research has focused on treatment of Borderline Personality Disorder. DBT has been shown to be effective in reducing suicidal/self injurious behaviors, and number of hospitalizations (22). Studies of the efficacy of DBT are ongoing in patients with substance abuse, eating disorders, and depression.

18.7 Family Therapy

This focuses on the family system as a whole. Family therapy views the functionality of the system as a whole to decipher individual behavior patterns amid complex interactions within the family system. It assumes people are best understood as operating in systems and treatment must include all relevant parts of the system. While many clinicians view families as an important aspect of understanding individual illness and treatment; others view family disequilibrium as the core issue, with individual illness a result of or solution to such disharmony (23).

Von Bertalanffy's concept of "general systems theory" introduced principles that provide an organismic approach to understanding biological beings. General systems theory applies to biological processes of considerable complexity since any living system must have boundaries in order to regulate its exchange with systems outside of itself. Over the years, general systems theory has been applied to the assessment of family systems and subsystems that also must have clear boundaries to stay functional. Further work by Minuchin helped define a continuum of families ranging from enmeshed (with permeable and diffuse boundaries) to disengaged (inappropriate rigid boundaries). Families with clear boundaries lie in the middle of this continuum and are considered the most functional. A significant related concept is that of "Family homeostasis," by which as a system, the family unit attempts to maintain a relatively stable state; when subjected to an incongruent force, it tries to restore back to a state of pre-existing equilibrium (24).

While conducting a comprehensive initial evaluation, a convenient tool used for family assessment is the three-generational genogram. Initially developed by Bowen, this genogram maps family relationships and provides a structure with which difficulties are explored by the therapist. During the initial phase of treatment, the therapist tries to better understand family strengths, preferred styles of thinking, contributory cultural issues, and the life cycle phase for the family. Furthermore, the therapist establishes and strengthens therapeutic relationships, defines goals of therapy, and switches focus from the individual to the family. The middle stage, where majority of therapy "work" happens, is an attempt to bring about change. This middle stage focuses on goals defined as primary. These goals could involve persistently inflexible patterns of family functioning, definition of family boundaries, or presentation of alternative modes of interacting for the family. The termination phase involves a review with the family of goals that were or were not achieved. The original problems and alternatives suggested are revisited and often the sequences leading to the pathology are reconstructed. The therapist also acknowledges problems may arise in the future and suggests how the family might then use skills they learned to help solve any such future conflicts (25).

Therapists use other techniques to assist dysfunctional families. Reframing involves the therapist understanding the patient's or family's perspective or frame and countering this frame with another alternate view. Enactment involves the playing out of the family problems

in the session. Boundary making is utilized to change the psychological distance between family members. Unbalancing techniques are used to change the hierarchical relationship of members of a family system or subsystem. Paradoxical techniques are occasionally used to make the family unit understand why a symptom is being maintained in their system (24, 25).

18.8 Couples Therapy (CT)

Psychotherapists experienced in couples therapy can assist in a number of ways (24). Therapy can help couples perceive and appreciate differences in ongoing individual challenges and the struggles rotted in the relationship. The life history of each person in couples therapy is important as is the history of the relationship itself. Different values, assumptions, and expectations may not be intentional, much less, personal. Mundane concerns over children, careers, and life transitions often stir up misunderstandings, stress, and unnecessary stress between couples. Thus, couples in therapy may gain perspective, learn new skills, discuss struggles and resentments without rancor. Couples' issues often include intimacy, power, decision making, parenting, leisure activities, and miscommunication (24). Outline of CT Sessions: Psychodynamic review of problems with either one or both partners can address misunderstandings that inevitably arise when two families unite formally in marriage or informally by way of sustained intimacy. In practical terms, both partners are usually seen together by two co-therapists at weekly to monthly intervals for an average of 6-10 sessions of 1-1$\frac{1}{2}$ hours. Clinical Applications: To resolve conflicts, couples must confide in a therapist to safely explore sources of and possible solutions to problems or failings in the relationship. Such exploration needs to be taken up in an open, understanding, reassuring manner in order for a couple's relationship to heal and grow. One or both in a couple may harbor concerns that inhibit their acceptance of therapy. Unstated fears often persist that a psychotherapist will be judgmental or partisan. Similar fears that the therapy will drive the couple apart rather than draw them closer commonly occur. One partner may fear that a shameful or guilt-ridden secret will be uncovered. Stigma for having marital problems is a frequent anxiety. However, not only is seeking out help is a healthy sign of maturity and hope rather than insecurity, it can be the basis upon which a couple may renew trust, esteem, and conviviality (24).

18.9 Supportive Therapy (ST)

Supportive psychotherapy is the most widely practiced form of individual psychotherapy today. As such, supportive psychotherapy is a general term for widely used techniques that improve, if not optimize, adaptation by way of directly addressing situational stress, such as chronic illness—mental or somatic—as well as acute stress as with bereavement. Supportive psychotherapy often spans a long term with brief contacts, although it can take a limited form of more extended sessions within a brief period (26). Outline of ST Sessions: The general framework of supportive psychotherapy include attention to indications and patient selection, treatment phases, session management, professional boundaries, as well as a wide range of issues in the therapeutic relationship, e.g., therapeutic alliance,

transference, countertransference, and therapist self-disclosure. The synthetic nature of supportive psychotherapy can be conceptualized across four major areas (26):

- Establishment and maintenance positive therapeutic alliances
- Formulation of patient problems, i.e., how to come to a thorough understanding for patient evaluation and case formulation)
- Targeting realistic treatment goals for and with patients, i.e., help maintain or reestablish best possible levels of patient function in the face of limitations to do with personality, talent, and existential circumstances
- Fluency in expressions to patients, i.e., practical techniques of immediate and frequent use.

Clinical Applications: Supportive psychotherapy is actually a continuum from merely supportive efforts such as a case manager may use, toward more expressive psychotherapy appropriate to the level of patient psychopathology and resilience. Supportive psychotherapy is especially pertinent for patients vulnerable to psychotic regression in the course of non-directive psychodynamic psychotherapy, or who have limited capacity to forge and sustain close relationships, or who are less skilled at verbalizing distress. Regardless of the clientele, essential aspects of supportive therapy include close attention to and elicitation of expressed emotions as "ventilation" as well as possible insight. It also includes overt explanation and education by the therapist to assist patient understanding of themes, struggles, and conflicts in their lives in order to facilitate confidence that such difficulties can be overcome. Similarly, supportive psychotherapy can entail open expressions by the therapist that are intended to boost confidence or restore morale. Supportive psychotherapy also often includes counseling advice or direct recommendations about specific problems.

18.10 Group Therapy (GT)

Every human being is raised in group environments. In fact, there are multiple groups interacting with any individual—families, schools, religious or social clubs, or work. Group psychotherapy can address inadequacies acquired in earlier group experiences from childhood through adolescence and beyond. In group therapy, patients join together with others to share problems or concerns, to better understand themselves and others, and to learn from and with others. It helps patients enhance interpersonal relationships and otherwise learn about themselves. It mobilizes feelings of isolation, depression or anxiety that the group and/or leader can help interpret so patients may make significant change and feel better about the quality of their lives (27). Outline of GT Sessions: For over 60 years, group therapy has been widely used as a standard treatment to help group members share and resolve problems of their own as well as those of their group peers. Group psychotherapy entails a small number of people (generally no more than eight or ten) who meet together regularly (most often weekly) under the guidance of one (or sometimes two) therapists (28). Clinical Applications: Supportive, behavioral, cognitive, and psychodynamic approaches arise in the course of group therapy. Most commonly, dynamic group therapy fosters a wide variety of transference relationships than is likely in individual therapy. Group therapy has given rise to a great many permutations that include more didactic or focused therapeutic themes. For example, anxiety management or social skills groups combine cognitive and behavioral techniques to treat specific problems common to all group members. Self-help

groups such as Alcoholics Anonymous frequently rely on techniques of group dynamic that also build a supportive and instructive milieu. Moreover, principles of group therapy and group dynamics underlie broader applications in other settings such as business consultation, schools management, and community organizations.

18.11 Patient Selection

No clear rules govern the referral of patients to particular modes of psychotherapy. Still, the suitability of particular patients for particular therapeutic techniques can be broadly outlined. Some basic principles of selection are:

- Patients who are vulnerable to psychotic breakdown are unsuited to non-directive approaches
- Patients who have little capacity of making and sustaining relationships
- Patients who are less verbally able are also relatively unsuited to non-directive approaches.

Psychotherapy can redress problems in prior critical learning periods. One such critical learning period is early childhood (about 2 to 5 years). Heinz Kohut emphasized that here, parents or other adults "mirror the grandiose self" of the child (28). This grandiosity derives from how children are (or should be) surrounded by praise and love with every minor achievement warmly applauded. However, as is all too clear in any psychiatric clinic, not every child had sufficient such tonic boosting to inure solid self-image. Indeed, many exit childhood sensing that they are unwanted, fundamentally bad, or failures or less favored than a sibling, and so on.

A second critical learning period for self-esteem is adolescence when parental influences wane or even become negative, while peer group influences become vital and avidly sought as peer group acceptance fosters high self-esteem. Yet many adolescents are rejected by their peers—they may be unattractive, disabled, or newcomers to an area where the peer group is "full" and does not require or even stigmatizes new arrivals. Such rejection by peers can further compound low self-esteem acquired early childhood or even efface high self-esteem previously engendered by parents. Self-esteem is difficult to alter after adolescence. It is true that important life events may have effects both positive, such as success in college or career, or negative as in being rejected by a desirable college or failing in a career. But in the clinic many successful, happily married people still have problems ensuing from bad experiences in early childhood or adolescence. It takes a time and effort to substantially improve self-esteem.

Ferdo Knobloch recognized the value of "corrective experience," elaborating ideas of Alexander and French (29) who saw how therapy can offer a re-run of bad experience. Knobloch (30) noted how individual psychotherapy can refurbish defects in the original parent/child relationship when, over a long course of care with a reassuringly supportive therapist, the patient can overlay bad early learning with newly positive experiences. Such therapy emphasizes the importance of childhood experiences as the therapist adopts aspects of the role of parent via patient transference. Here the good therapist is able to elevate the patient into something of an equal, in the way that a good parent eventually assists a child to separate and individuate as a health, self-actualized adult.

However, if low self-esteem arose in negative adolescent experiences, individual therapy cannot effect a re-run. Parent figures are importent at this stage. What is instead needed is a re-run with a group that represents the adolescent peer group. This re-run can most effectively be achieved with group therapy, as other treatment group members understudy the role of adolescent peers. Here transference is not to the therapist but to the peer group as a whole.

18.12 Summary

Research that spans neuroscience and psychoanalysis is rapidly enhancing the scientific foundation of all types of psychotherapy as insights accrue concerning critical learning periods, narrative capacity, and neuroscientific discoveries in of existential adaptation. In practical terms, the sequelae of negative childhood events are perhaps best addressed by individual therapy whereas those due to adversities in adolescence are likely to benefit from group therapy. It is less widely appreciated but quite important to appreciate that such research also directly links psychotherapy to evolution, particularly the emotive and rational capacities and reactivities of highly social species such as Homo sapiens. Most patients are able to give a clear account of how they felt about themselves in childhood and adolescence, and these reports should be taken into account in deciding between individual and group therapy as well as in guiding the course of any dynamic therapy toward the resolution of and recovery from problems in living.

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19 The Agitated/Violent Patient

Nelson Mandela discusses violence by saying "This suffering ... is a legacy that reproduces itself, as new generations learn from the violence of generations past, as victims learn from victimizers, and as the social conditions that nurture violence are allowed to continue. No country, no city, no community is immune. But neither are we powerless against it" (WHO, 2002).

Few people have not been touched by violence of one form or another, whether it be directly toward the individual or towards persons who are somehow connected to the individual. It shapes decisions we make and impulses on which we act. Those who have been more personally influenced by violence may become chronic victims or abusers although those who experience violence from a distance may also react in an life altering way, for example persons who were not at the 9/11 Twin Towers disaster but heard it on the radio or saw it in the news who developed post traumatic stress syndrome or agoraphobia

In the words of GH Brundtland, Director –General of the World Health Organization (WHO), "Violence pervades the lives of many people around the world, and touches all of us in some way. To many people, staying out of harm's way is a matter of locking doors and windows and avoiding dangerous places. To others, escape is not possible. The threat of violence is behind those doors – well hidden from public view. And for those living in the midst of war and conflict, violence permeates every aspect of life" (WHO, 2002).

19.1 Phenomonology

Definitions of violence and related words are used interchangeably in the literature, leading to some confusion. Violence and aggression are both terms used to denote force used against someone or something. Merriam-Webster on-line dictionary cites one definition of violence as "exertion of physical force so as to injure or abuse" and a similar definition of aggression as "a forceful action or procedure (as an unprovoked attack) especially when intended to dominate or master." Citrome and Volavka (2003) discuss aggression, violence, and hostility and define aggression in terms of both human and animal "overt behavior involving intent to deliver noxious stimulation to another organism or to behave destructively toward inanimate objects." Violence they define as exclusively human, including only physical aggression of one human against another.

19.2 Epidemiology

In 2002, the WHO"s report estimated 1.6 million people lost their lives to violence in 2000. Half of the deaths were suicide, a third were homicide and one-fifth were casualties of conflict

(WHO, 2002). Males had higher rates of homicidal death than females, and the 15-29 age group had the highest rates of the male population (WHO, 2002). Rates tended to decline with age. Rates of violent death also varied by country. Rates were higher in low to middle income countries when compared to higher income countries (WHO, 2002).

19.3 Clinical Symptoms and Classification

Modified from WHO report 2002.

A second classification system that is also in use was developed by K. E. Moyer. It includes: Preditory aggression Inter-male aggression Fear-induced aggression Irritable aggression Maternal aggression Sex-related aggression

19.3.1 Assessment

Violence risk assessment is not an exact science. Psychiatrists have only been able to assess violence with moderate accuracy (Woods and Ashley, 2007). Statistically, the greatest risk factor for violence is past violence. Accurate risk assessment must take into account statistical risk factors, such as past violence, as well as individual factors (Woods and Ashley, 2007).

Demographic and individual factors correlate with a higher risk of violence. Men have a rate of violence 10 times that in women (Scott et al.) Past violence is the single best predictor of future violence, and the use of violent weapons may predict use of future weapons (Scott et al.).

Substance use is highly correlated with violence and alcohol, amphetamine, cocaine and other drugs that lead to disinhibition or euphoria may preclude violence (Scott et al.). In populations of mentally ill individuals, substance abuse is strongly correlated with violence (Scott et al.).

The presence of psychotic symptoms has been extensively studied in violence risk and findings are inconclusive. In conducting a violence risk assessment, it is important to inquire regarding paranoia, and delusions that may cause a person to feel unhappy, as these may lead to violence (Scott et al.).

The interview itself should be held in an environment that is safe for the interviewer as well as the interviewee. Affective state or thought disorder abnormalities may put the interviewer at increased risk and may have to be dealt with prior to a formal interview. Patients with violent thoughts should be asked about any specific plan, what kind of violence (hurting vs killing), and whether the plan could be carried out against the possible victim (i.e., access to a gun, victim living in the same town etc.).

Major Violence Risk Factors	
Prior arrests	**Demographic**
Seriousness	Age (-)
Frequency	Male
	Unemployed

Major Violence Risk Factors	
Prior arrests	**Demographic**
Child abuse	**Diagnosis**
Seriousness	Antisocial Personality Disorder
Frequency	Schizophrenia (-)
Father	**Other Clinical**
Used drugs	Substance Abuse
Home until 15 (-)	Anger control
	Violent fantasies
	Loss of consciousness
	Involuntary status

Adapted from: `http://macarthur.virginia.edu/risk.html`

19.3.2 Pathogenesis

"Most perpetrators of aggressive behavior (criminal or otherwise) are not mentally ill, and aggressive behavior cannot be explained by biological factors alone. In fact, most of the aggressive behavior observed in daily television newscasts is perpetrated by terrorists and other criminals who may not have any discernible biological predisposition to violence" (Citrome and Volavka, 2003) .

Biological factors

Non-Psychiatric Diagnoses
Prior to a psychiatric diagnosis being sought for aggressive and violent behavior, somatic complaints should be ruled out. These would include such things as underlying metabolic, toxic, or infectious conditions. A handy mnemonic that has been developed for life threatening causes of aggressive behavior is the one adapted for Wise (1987). It is **WWH-HHHIMPS** and stands for **W**ithdrawal from barbiturates and other sedative-hypnotics, **W**ernicke's encephalopathy, **H**ypoxia, **H**ypoperfusion of the brain, **H**ypertensive crisis, **H**ypoglycemia, **H**yper/hypothermia, **I**ntercranial bleed/infection, **M**eningitis/encephalitis, **P**oisoning, **S**tatus epilepticus. Testing may include routine chemistry, oxygenation measurement, blood counts, serum and or urine toxicology, an organic work-up for dementia, neuroimaging, electroencephalogram (EEG) or other radiological tests as indicated.

Psychiatric Diagnoses
As noted above, violence and aggression are associated with subsequent onset of mood and anxiety symptoms, as well as full depressive and post-traumatic stress disorders. However, mood disorders have also been identified as a precursor to the onset of aggression. The presence of a mood disorder increases the likelihood of an individual being a victim of violence (Brunstein Klomek et al. 2007; Lehrer et al. 2006), and the perpetuator of violence (Brunstein Klomek et al. 2007).

Depression in adolescents is one of the major predictors of aggression or violence (violence being a more extreme form of aggression) (Teicher et al. 2006; Blitstein et al. 2005), or

oppositional and delinquent behaviors (Rowe et al. 2006). Major depressive disorder and bipolar disorder are both associated with an increase in irritability, aggression, and potential violence against others and self (Najt et al. 2007; Grunebaum et al. 2006; Schuepbach et al. 2006; Knox et al. 2000; North et al. 1994). Bipolar illness, in particular, may be associated with aggression due to the nature of its core symptoms of irritability, lability, grandiosity and paranoia (Feldman, 2001; Swann, 1999).

Bipolar patients admitted involuntarily to an inpatient unit were more likely to have comorbid substance abuse, and up to three times more likely to be aggressive after admission (Schuepbach et al. 2006; Barlow et al. 2000). An analysis of 576 consecutive admissions for mania suggested that acute mania may be characterized by four distinct phenomenological subtypes; these include pure, aggressive, psychotic, and depressive (mixed) mania (Sato et al. 2003). When a patient's illness recurs, the profile of symptoms, including aggression, remains relatively consistent (Cassidy et al. 2002), supporting the clinical notion that there is a high association between past and future violence. The increase in aggression associated with mania is associated with an increase in legal problems. While patients with schizophrenia or schizoaffective illnesses are more likely to be arrested (Grossman et al. 1995), patients with bipolar disorder are more likely than unipolar depression to have legal problems (Calabrese et al. 2006). At the time of their arrest a large number of bipolar subjects were manic (74.2% of 66 subjects studied) or psychotic (59%) (Quanbeck et al. 2004). Many of these patients have already come to the attention of the health care system and had recently been discharged from an inpatient unit, but had not attended their outpatient follow-up (Quanbeck et al. 2004). This may explain why bipolar subjects are over-represented among sex offenders, with approximately 35% of sex offenders having a bipolar disorder (usually with comorbid antisocial personality disorder or substance abuse) (McElroy et al. 1999; Dunsieth et al. 2004).

However, aggression can also occur during depressive episodes. In bipolar patients, aggression can be a relatively common presentation of agitated depression (Maj et al. 2003). Aggression is also common in unipolar depression (Posternak and Zimmerman, 2002). A syndrome of high irritability and other hypomanic symptoms in unipolar depressed patients has been labeled mixed depression (Sato et al. 2005), which may be associated with significant aggression (Sato et al. 2005).

Other psychiatric disorders that should be considered include substance use (considering especially alcohol, psychostimulants, hallucinogens. Sedative-hypnotics, opiates, prescription medications such as anticholinergics and steroids), schizophrenia – especially with comorbid substance use, intermittent explosive disorder, attention deficit disorder, antisocial or borderline personality disorder, paranoid personality disorder and those with mental retardation or with dementia (DSM-IV TR).

Molecular level findings

Neurochemistry

Serotonin

On a molecular level, the serotonin system has been implicated in self harm and violent population studies. There are many biological associations between mood symptoms and aggression or violence. These include increased aggression with increased cytokine activity

(Zalcman and Siegel, 2006), catecholamine metabolism (Volavka et al. 2004), testosterone (Pope et al. 2000), and hypothalamic-pituitary-adrenal axis dysfunction (Shea et al. 2005; Malkesman et al. 2005). However, the most consistent findings are with the serotonergic system. Among the many findings associated with serotoninergic dysfunction in aggression, platelet serotonin 2A receptor (5-HT2A) binding was increased in subjects with trait aggression (Lauterbach et al. 2006). Prefrontal cortical 5-HT2A binding was also increased in aggressive suicidal patients (Oquendo et al. 2006). Similarly, relative increases in plasma tryptophan levels (a precursor to serotonin) are associated with increased aggression and hostility (Lauterbach et al. 2006; Suarez and Krishnan. 2006) Lower CSF 5-HIAA concentration was independently associated with severity of lifetime aggressivity and a history of a higher lethality suicide attempt and may be part of the diathesis for these behaviors. The dopamine and norepinephrine systems do not appear to be as significantly involved in suicidal acts, aggression, or depression (Placidi et al. 2002). However, the most compelling findings regarding the involvement of serotonin in both mood disturbance and violence is found in the serotonin transporter polymorphisms.

Several recent studies have investigated the role of polymorphisms in the serotonin reuptake pump or the serotonin transporter gene (5HTTLPR). A common polymorphism of this gene is a deletion in the area of the gene that regulates its transcription into messenger RNA, and ultimately translation into expressed protein, the promoter region. Individuals with this deletion, called the short or "s" allele, express fewer serotonin transporters. Individuals who are homozygous for the "s" allele (ss), are more likely to develop depression (OR 1.5-179) (Cervilla et al. 2006) and depression after a traumatic event (Kaufman et al. 2004; Caspi et al. 2003). Thus, the observed link between early life adversity, or later life trauma, and subsequent depression, is related, at least in part, to having the ss genotype (Kaufman et al. 2004; Caspi et al. 2000). While stressful life events or extreme adversity are clearly associated with subsequent depression, adversity is quite potent in inducing depression in subjects with the ss genotype; so that the dosage of adversity required to produce depression is much lower in individuals homozygous for the short form of the 5HTTLPR (Cervilla et al. 2007). Several studies have also found that the ss genotype is also associated with subclinical depressive symptoms in individuals without depression (Gonda et al. 2005, 2006; Gonda and Bagdy, 2006).

The ss genotype of the 5HTTLPR is also associated with aggression. In a case control study of conduct disorder with or without aggression, it was found that the ss genotype was strongly associated with aggression but not conduct disorder without aggression (Sakai et al. 2006). A positron emission tomography (PET) study of 5HRRLPR density found that reduced transporter density is associated with impulsive aggression (Frankle et al. 2005). While this study did not examine the genotype of the study subjects, it found that the phenotype that is expected with the ss genotype is associated with aggression (Frankle et al. 2005). Among schizophrenic patients who attempted suicide, the ss genotype of the 5HTTLPR was associated with violent suicide attempts but not with non-violent attempts nor with non-attempters (Bayle et al. 2003)

Neuroanatomy

There is no center in the brain that has been identified as associated with aggression, however there are areas that have been identified in animals as being activated in excitatory or inhibitory ways during aggressive behaviors. These include the hypothalamus, the limbic

system and the prefrontal cortex. Disorders associated with these areas of the human brain are more often associated with violent behaviors.

Psychological Factors

Passive Exposure to Violence

Witness to Domestic Violence

Early life experiences can affect both the biology and behavior of an individual. For example, abuse or neglect of young individuals will influence the development of mood disorders and problem behaviors later in life. Miller (2005) reports that childhood abuse and exposure to trauma may be linked in increased production and secretion of cortisol and epinephrine, which have been linked to depression and anxiety. Research also suggests that infants exposed to domestic violence between their parents can exhibit signs of trauma and some behavioral problems, such as aggression (Bogat et al. 2006; Whitaker et al. 2006). However, Bogat et al. (2006) suggest that passive exposure to parental violence does not alter an infant's temperament.

As children grow older, passive exposure to violence between their parents can have more dramatic effects. As many as 10-24% of children may be exposed to intimate partner violence (IPV) between their parents, or other family violence (Martin et al. 2006; Silverstein et al. 2006). Martin et al. (2006) maintain that exposure to violence occurs prior to age 11 in 80% of families with IVP. If community violence is included, the rate of adolescents who have witnessed violence may be as high as 40% (Hanson et al. 2006). Prevalence rates of depression and anxiety are increased in adolescents and young adults (age 13 to 21) who experience passive exposure to IVP (Hindin and Gultiano, 2006; Martin et al. 2006). Young women may be at greater risk than young men (Hindin and Gultiano, 2006). In addition, Hazen et al. (2006) report that problem behaviors increase in children aged 4 to 14 who experience passive exposure to IVP in the home. Behavioral problems span both internalizing problems (depression, low self-esteem, etc.) and externalizing problems (aggression, acting out, etc.) (Hazen et al. 2006). These effects are independent of maternal depression (Hazen et al. 2006; Martin et al. 2006). This is an important observation, since maternal depression is associated with an increase in adolescent depression and school dysfunction, but not an increase in problematic behavior (Peiponen et al. 2006; Silverstein et al. 2006). Sternberg et al. (2006) found that exposure to family violence in older children, aged 10 to 16 years, also increased subsequent depression and behavioral problems; this effect was greater for girls than boys.

Parental Substance Abuse

Parental substance abuse can result in both direct and indirect problems for children. At the very least, children of substance abusing parents are neglected. However, more frequently, substance abuse is associated with a variety of factors that independently or in combination can be quite harmful. These include domestic violence and several forms of abuse, including verbal, emotional, physical and sexual abuse. Parental substance abuse is associated with an increased risk of depression, aggression, behavioral problems, and substance abuse in the children (Edwards et al. 2006; Hanson et al. 2006; Peiponen et al. 2006; Whitaker et al. 2006; Sher et al. 2005).

Social and Cultural Factors

Direct Abuse or Neglect

Childhood abuse and neglect are clearly associated with a substantial increase in the risk for subsequent depression and maladaptive behaviors (Cukor and McGinn, 2006; Reigstad et al. 2006; Widom et al. 2007) as are adult abuse and neglect. This is true in all cultures in which it has been studied (Afifi, 2006).

Verbal and Emotional Abuse. The experience of verbal abuse during childhood (e.g., "you are stupid") increases depression, anger and hostility in young adults (Teicher et al. 2006; Sachs-Ericsson et al. 2006). Verbal and emotional abuse influence the development of self-concept, and lead to a self-critical style of cognitive processing that contributes to low self esteem (Cukor and McGinn, 2006; Sachs-Ericsson et al. 2006). This impaired self-image may be one of the underlying phenomena that increase the risk of subsequent sexual victimization as a young adult (Rich et al. 2005).

Physical Abuse. Physical abuse may be a major contributing factor in the development of violence in later life (Huizinga et al. 2006). Physical abuse is also pivotal in the development of depression in youths and on into adulthood (Widon et al. 2007; Cukor and McGinn, 2006; Reigstad et al. 2006; Wright et al. 2004). Physical abuse may occur in either the home environment or in school. Bullying is a form of verbal and physical violence that can have major impact on development. The odds of experiencing social problems, depression with suicidal ideation and attempts are 3.9 times higher among victims of bullying compared to non-victims (Brunstein Klomek et al. 2007; Kim et al. 2006). Furthermore, bullying behaviors have been linked to mood disturbances. The odds of bullies developing social problems, depression, and suicidality are 1.8 times higher compared to people who are not bullies, and bullies who are also targets of other bullies are 4.9 times as likely to develop social problems (Brustein Klomek et al. 2007; Kim et al. 2006). High profile school shooters, such as Columbine High School or Virginia Tech University, have been bullied by class mates.

Sexual Abuse. Sexual abuse of children is associated with a wide variety of physical and psychological sequelae, many of which are life-long. Early sexual abuse is associated with a significant increase in depression in both males and females (Peleikis et al. 2005; Conway et al. 2004; Gladstone et al. 2004; Martin et al. 2004). The risk of subsequent suicide attempts is 15 times higher in boys who experience early sexual abuse compared to non-abused boys (Martin et al. 2004); among women suicide ideation is 4.5 times higher (Masho et al. 2005). The consequences of childhood sexual abuse include greater severity of depressive illness in adult patients over age 50 (Gamble et al. 2006; McGuigan and Middlemiss, 2005). Adult women who have experienced childhood sexual abuse are more likely to be victims of violence (Gladstone et al. 2004) and other forms of trauma, including sexual assault (Rich et al. 2005; Banyard et al. 2002). Sexual abuse perpetrated by adult women can be just as harmful as sexual abuse perpetrated by men (Denov, 2004).

Adult Assault. After personality development is complete, adult assaults (sexual or physical) can increase the likelihood of the development of mood disturbances (Johansen et al. 2006). Consequences of being a victim of assault include depression, anxiety disorders, and substance abuse; these can persist for decades (Acierno et al. 2007).

Substance Use. Alcohol and illicit drugs are involved in a large number of abuse situations. Kyriacou et al. (1999) reported that 51.6 women who had been injured during an assault by a male partner had reported that the partner had alcohol on board at the time of the assault. In males arrested in the United States, it was reported that urine tests for illicit drugs was positive in the majority of the males (Pastore and Maguire, 2000).

Intimate Partner Violence. Intimate partner violence (IPV), perhaps the most common type of violence in our society, is pervasive throughout several socioeconomic classes and ethnic groups. Thirty percent of African American women seeking medical care in a large public hospital reported severe IPV (Paranjape et al. 2007), and 54% of women attending a rural family practice clinic reported IPV (Coker et al. 2005). Researchers have estimated that 10-24% of representative samples of children may be exposed to IPV (Martin et al. 2006; Silverstein et al. 2006). In addition, 13% of middle class women also have experienced IPV (Anderson et al. 2002). Exposure to IPV is associated with a significant increase in the risk for both depression and PTSD (Paranjape et al. 2007; Avdibegovic and Sinanovic, 2006; Bonomi et al. 2006; Houry et al. 2006; Varma et al. 2006; Lipsky et al. 2005), as well as greater medical problems, reduced functioning, and increased medical disability (Bonomi et al. 2006; Coker et al. 2006). Depression risk is almost 6 times higher in women who are victims of IPV compared to those who are not, and PTSD is 9.4 times higher (Houry et al. 2006). Sexual IPV is specifically associated with an increase in depression and suicide ideation (Pico-Alfonso et al. 2006); Houry et al. (2006) have observed that suicidal ideation in women who have experienced IPV is 17.5 times higher compared to women who have not experienced IPV. However, depression frequently predates the episodes of IPV, and the presence of depression in young women actually increases the likelihood of dating-violence (Rivera-Rivera et al. 2006; Foshee et al. 2004). African-American women may be at particular risk for mood disturbances due to high rates of IPV; 18% also abuse alcohol, which can worsen prognosis (Paranjape et al. 2007). Women in abusive relationships have a great need for emotional support (Theran et al. 2006), and African-American women appear to obtain much support through spirituality and affiliation with religious institutions (Mitchell et al. 2006; Watlington and Murphy, 2006).

Community Violence/War/Terrorism

Although violence at a personal level is a major factor in the development of mood disturbances, violence at the community level also contributes to subsequent depression, suicidal ideation, and suicide attempts. For example, community violence can increase the risk of depressive symptoms in adolescents, particularly girls (Goldstein et al. 2007; Hammack et al. 2004). Terrorists count on the psychological impact of indirect violence to achieve their aims. After the September 11th, 2001 attacks in New York and Washington, DC and the March 11th, 2004 attack in Madrid, Spain, prevalence rates of major depression increased (9.4% in New York City and 8% in Madrid, compared to 6.4% in population-based surveys [Kessler et al. 2006]), and to a lesser degree, PTSD (Person et al. 2006; Miguel-Tobal et al. 2006). This increase was also associated with a 49% increase in suicide attempts along the East coast of the United States after the September 11th attacks (Starkman, 2006). Gaylord (2006) estimates that 10-17% of combat veterans will experience psychiatric problems, including PTSD and depression. These disorders may last for long periods of time after the end of hostilities (Fiedler et al. 2006). However, among civilians who are trapped in war zones, or are direct targets of attacks or abuse, rates of PTSD have been estimated at

almost 33%, and rates of depression are approximately 41% (Hashemian et al. 2006; Loncar et al. 2006).

19.4 Treatment

Treating Victims

Pharmacotherapy: Pharmacologic approaches to treatment of victims are geared towards treating the depression and PTSD that may be associated with past or current exposure to violence.

Psychotherapy: Researchers have investigated the effectiveness of various forms of psychotherapy in the treatment of depression and PTSD resulting from exposure to violence; these include supportive therapy, cognitive behavioral therapy (CBT), and forgiveness therapy (Deblinger et al. 2006; Reed and Enright, 2006). Focused therapies such as CBT or forgiveness therapy appear to be more effective than unfocused supportive therapy (Deblinger et al. 2006; Reed and Enright, 2006). Forgiveness therapy has been central to national attempts at healing past abuse such as the South African Truth and Reconciliation Commissions (Potter, 2006). Adult treatment for childhood abuse is effective in reducing symptoms and dysfunction (Martsolf and Draucker, 2005). The approach for women involved in IPV depends on the timing of the abuse. Women in a current abusive relationship benefit more from emotional support, while women with past abuse require practical support (Theran et al. 2006).

For adults, initiation of therapy for depression and PTSD after years of exposure to violence suggests that treatment may have been started too late on an illness trajectory. Prevention is a critically important focus for those at risk for developing violence-related mood disturbances. Identification of children at greatest risk due to violence or substance abuse in their families, and provision of appropriate support to prevent depression, aggression, substance abuse, and future victimization, would be the ideal approach (Sternberg et al. 2006). Past abuse predicts future abuse; policymakers can use this knowledge to direct appropriate resources towards prevention of future abuse among those at risk.

Treating Aggressors

Pharmacotherapy: The effect of antidepressant medications in the treatment of aggression is unclear. Antidepressant treatment has been variously reported to increase and decrease aggression (Goedhard et al. 2006; Healy et al. 2006; Bond, 2005; Mitchell, 2005). If there is an anti-aggression effect of antidepressants, it is weak (Goedhard et al. 2006). An increase in aggression associated with antidepressant use may possibly occur exclusively in individuals with bipolar disorder or occult bipolar disorder, i.e., those in which an episode of mania has not yet occurred.

Antipsychotic medications or mood stabilizers are generally used to treat aggression (Barzman et al. 2006; Afaq et al. 2002). Valproate is perhaps one of the best studied agents, and found to be superior to other anti-epileptics, such as topiramate (Gobbi et al. 2006) or oxcarbazepine (MacMillan et al. 2006) A meta-analysis of controlled trials suggests that the

effect of these interventions is generally small (Goedhard et al. 2006). Dopamine antagonist antipsychotic medications may be minimally better than serotonin-dopamine antagonist medications (Goedhard et al. 2006). Effective pharmacologic treatment approaches to reduce aggression and violence in those with mood disturbances are greatly needed.

Beta-adrenergic blockers, most often propranolol, have been used to treat aggression in brain injured patients (Yudofsky et al. 1981). Benzodiazepines, especially clonazepam and lorazepam have been used for long term management of aggression. Both are problematic in terms of psysiological tolerance and in terms of withdrawal if missing doses.

Psychotherapy: Psychotherapy has been shown to be helpful with some types of nonpsychotic patients with violent behaviors. Those interventions most helpful are cognitive-behavioral therapy and dialectical behavior therapy (Meichenbaum and Goodman, 1971; Linehan, 1987).

19.5 Case Studies

Mrs. H *Mrs. H is a 47 year old married mother of two college-age children who presented to the emergency department after falling down the stairs at home. She complained of a pain in her arm, shoulder and ribs. An xray revealed a non-displaced fracture of her humerus and a broken rib. She was splinted, and followup was arranged for the orthopedic clinic the next day. Her husband had been at her bedside during the evaluation process and refused to leave her side. He appeared attentive and caring. When he left to get the car, Mrs. H told the nurse, "I'm afraid he will kill me next time." Mrs. H had married her husband when she became pregnant at age 17 and dropped out of high school. They had struggled financially for many years until he was promoted to foreman at his construction company. She stayed home with the children and had few social contacts. Her husband often went to the bar after work with his co-workers and she described him as an "angry drunk."*

Mrs. H had never seen a psychiatrist. A psychiatric consult was ordered when she became tearful while describing the event to her ER nurse. On mental status exam, she endorsed symptoms of social isolation, depressed mood, poor sleep, tearfulness and feeling hopeless. She reported that she had been feeling this way for "a long time." Mrs. H's husband became furious when he returned to the ER and saw her talking with the psychiatrist. He told her, "either you come with me now or I won't let you back in the house." She decided to stay at the hospital and was discharged to a shelter for battered women. She participated in individual and group therapy, and started on fluoxetine to treat symptoms of depression. She decided to press charges against her husband and eventually filed for divorce.

1. What clues in Mrs. H's presentation should have raised suspicion for domestic violence?

2. What are the elements of a comprehensive treatment plan for this patient?

Mr. M *Mr. M is a divorced, 33 year old man with no psychiatric history who was court ordered to psychiatric treatment after getting into an altercation with a co-worker that led to assault charges. He reported "mood swings" since his late teens when he began experimenting with marijuana. He admitted to occasionally using cocaine on weekends and drinking alcohol to "wind down." During review of psychiatric symptoms, Mr. M met DSM IV criteria for bipolar disorder. Upon further questioning, the psychiatrist discovered that he had experienced*

multiple periods of several days duration, in which he went without sleep and indulged in increased partying behaviors that ended in a "crash."

Mr. M had been raised by his mother. His father was an abusive alcoholic and left when he was four years old. Mr. M did poorly in school and ended up dropping out in the 11th grade because he was tired of being bullied and called "stupid." Mr. M's psychiatrist started valproic acid, a mood stabilizer, and recommended weekly psychotherapy aimed at developing coping skills to deal with anger. After 12 weeks of treatment, Mr. M was experiencing fewer mood swings and felt as if he could deal with frustrations in a more healthy manner.

1. What risk factors does Mr. M have for development of violent behaviors?

2. What additional treatments or therapies could be included in formulating a comprehensive treatment plan for this patient?

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20 Self-harm and suicide

Self harm is commonly used by psychiatrists and mental health professionals to describe a wide variety of behaviors that may or may not be related to suicide. Both self harming behaviors and suicide permeate society around the world and across demographics. Suicide is defined as self inflicted death with evidence that the person intended to die according to APA practice guidelines. Self harm is more difficult to define because its causes are poorly understood and the spectrum of behaviors can vary widely between individuals and between cultures. Behaviors commonly included in the self harm spectrum include overdoses, self battery, cutting, burning, poisoning, hanging and jumping from high places that do not result in death (Skegg, 2005). Suicide ultimately results in intentional self-inflicted death and self harm may lead to suicide.

The APA practice guidelines define terms related to self harm and suicide as the following:

Suicide self inflicted death with evidence that the person intended to die

Suicide attempt self injurious behavior with a nonfatal outcome and evidence that the person intended to die Aborted suicide attempt-potentially self injurious behavior with evidence that the person intended to die but stopped before physical damage occurred

Suicide ideation thoughts of serving as the agent of one's own death

Suicidal intent subjective expectation and desire for self-destructive act to end in death

Lethality objective danger to life associated with suicide action or method

Deliberate self harm willful self-infliction of painful, destructive or injurious acts without intent to die

Both of these phenomenons are important to clinicians to understand and be aware of because of their prevalence in the mental health patient population. An estimated 4.3 to 17% of the psychiatric patient population will engage in deliberate self-harm, with higher rates in some subgroups (Fliege, 2006). Self-harm and suicidal behaviors pose a significant public health burden and utilize a tremendous amount of hospital resources (Sinclar, 2006). Up to 40% of people who deliberately harm themselves will go on to become repeat offenders (Zahl, 2004). Treatment of chronic self-harmers can be frustrating to the treatment team due to the poorly understood nature of the behavior and high rates of repeat admissions. Many patients are managed in emergency departments or do not seek treatment after performing these behaviors. Management depends largely on the underlying pathology and controlled trials of therapies are limited (Skegg, 2005).

20.1 Phenomenology

Naming and classifying self-harm has been a topic of debate since the early 1900's (Skegg, 2005; Mcalister, 2003). Different terms that have historically been used to delineate self-harm behaviors include attempted suicide, parasuicide, deliberate self injury and deliberate self poisoning. Terminology can vary in different parts of the world and imply intent. Recent literature suggests that many who self-harm do so without suicidal intent (Skegg, 2005).

Skegg describes self-harming behaviors in a 2005 review on a spectrum from self-harmful behaviors without visible injury to highly lethal traditional methods of suicide. Excessive exercise, denying oneself as punishment, stopping medication or deliberate recklessness fall on the end of this spectrum without visible injury. Self battery behaviors include head banging, self-hitting or hair-pulling. Self-injury with tissue damaging behaviors include self-biting, scratching, gouging, carving words or symbols into skin, sticking needles or pins into skin and interfering with wound healing. At the other extreme less lethal traditional methods of non-intentional suicide include overdose, recreational drug ingestion as self-harm, cutting and burning. Traditional highly lethal methods of suicide include hanging, shooting, jumping from a high place, poisoning, stabbing, electrocution and drowning.

When considering these behaviors on a spectrum, it is important to consider intent. Traditional risk assessments correlate lethality with suicidal intent, however in a sample of survivors of near-fatal self harm, only two-thirds of patients experienced suicidal thoughts prior to the event (Douglas, 2004). The current consensus view is that those who self harm, despite how seriously, believe that they will survive (Mcallister, 2003). It is important to consider, however, that patients who harm themselves are more likely to go on to commit suicide than those who do not.

20.2 Epidemiology

Rates of self-harm and suicide vary widely around the world and have historically been difficult to quantify because many people do not seek medical attention after attempts and discussion of such behaviors is sometimes considered socially taboo. Birth cohort studies show higher odds for self harm in people born in recent years. The WHO/EURO study of parasuicide showed lower rates in southern European areas compared to northern areas (Skegg, 2005). In the United States, African Americans are at lower risk for self harm than other ethnic groups. Self-harming behaviors are common in adolescents and an estimated 5-9% of Australian, US and English adolescents reported self-harm over a one year period (Skegg, 2005). Lifetime self-harm ranged from 13-30% in these samples of adolescents (Skegg, 2005).

Skegg (2005) correlated demographic variables with risk of self-harm behaviors. It is rare before pubery and becomes common through adolescence. Older people are at much lower risk for self harm. More women than men present to mental health facilities with complaints of self-harm. Separated and divorced people appear to have higher rates of self-harm than other populations. Low socioeconomic status, less education and living in poverty are also risk factors for self harm (Skegg, 2005).

Further studies investigating suicidal behaviors are necessary to better understand the phenomenon and to create prevention strategies. Using three national medical databases, the annual rate of nonfatal emergency department treated intentional self-harm events in 2002-3 was between 127.2 and 164.7 per 100,000 US population (Classen, 2006). However, these rates do not include behavior of individuals not seeking treatment or seeking treatment in other medical facilities.

20.3 Clinical Symptoms and Classification

Vignette #1

Sue was a 25 year old female who presented to the emergency room with a 3cm laceration on her left wrist. The laceration was superficial but deep enough that it required sutures. There were multiple other superficial lacerations that did not require sutures as well as multiple healed scars from previous lacerations all up and down her forearm.

After Sue's wrist was sutured, she was evaluated by a psychiatrist for a possible suicide attempt. Sue revealed that she had been having a fight on the phone with her boyfriend and they had broken up. She denied any thoughts of suicide but rather said she was trying to reduce the tension and anger she felt about the situation. When asked about whether the self harm helped, she said it did release tension and therefore makes her feel more normal. She described it as a coping skill and did not see it as a problem behavior. She was discussing plans for going out with friends and maybe getting together with a boy who might want to be her new boyfriend.

Sue's past history is significant for sexual abuse at age 5 years by a cousin who was living with the family for the summer. Sue said she had always been sad and depressed but she did not endorse enough symptoms to qualify for a major depressive disorder. She said that she has a history of getting more depressed whenever someone left her or told her she was not making them happy. That was when she would cut on herself. She was very clear that she did not intend to kill herself during those times although she endorsed the idea that she might be better off dead than alive.

Sue was deemed to be safe to go home. She was referred to therapy to work on the issues that caused her to use self harming behaviors for comfort.

20.3.1 Assessment

Assessment of suicide and self harming behaviors takes place in a variety of treatment situations. It is often evaluated during an initial meeting with a patient in the emergency setting or at an outpatient intake. On an inpatient ward, assessment of suicide and self harm should be completed prior to advancement in privilege level, passes and discharge. If changes in the patient's presentation occur or if the patient begins to display evidence of suicidal or self harming thoughts, an assessment should be completed. The APA practice guidelines describe a thorough assessment of the suicidal patient.

During the interview, the psychiatrist obtains information about the patient's psychiatric history, medical history and current psychologic state through direct question and collateral

information. This enables the psychiatrist to make a risk assessment, determine the patient's current level of safety, choose an appropriate treatment setting and develop a treatment strategy. Suicide scales can be used to supplement the interview, but should not be used as a substitute because they lack the predictive validity to take the place of a thorough interview (APA practice guidelines).

A suicide assessment should include evaluation of current suicidal state, consisting of thoughts and plans regarding suicide. Specific methods should be elicited, including perceived lethality and access to firearms. The presence of hopelessness, guilt and anhedonia should be determined as well as reasons that prevent the patient from carrying out suicide plans. It should also include current and previous psychiatric illnesses including mood disorders, psychotic disorders, substance use disorders and anxiety disorders. Personal and family history of suicide and self harm behaviors should be noted, as well as outcomes. An individual's psychosocial state should be assessed to evaluate current stressors that could exacerbate suicidal behaviors, as well as cultural or religious beliefs that could be protective (APA practice guidelines).

It is important for the psychiatrist to collect as much information as possible regarding current suicidal or self harming behaviors. These include frequency and duration of thoughts, specific plans and preparation made to complete plans. Attention should also be given to prior attempts, including timing, intent, relation to substance use and outcome. If a specific method is identified as a current suicidal ideation, perceived lethality should be determined. Highly lethal and irreversible means with advance planning place an individual at increased risk. If firearms are involved, the psychiatrist should contact a friend or relative and have them removed from the patient's home before release (APA practice guidelines).

20.3.2 Pathogenesis

The pathogenesis of self harm and suicidal behavior is complicated and multifactorial. Sourander et al. (2006) attempted to identify early factors correlating with self-harm behaviors in childhood and adolescents. In this longitudinal study, parents rated children on Childhood Behavior Checklist and adolescents and their parents rated psychopathology at ages 12 and 15. Psychopathology in the child, poor parental well-being and living in a broken home at age 12 correlated with deliberate self harm at age 15. School and problems with peer groups at age 12 correlated with ideations of self harm at age 15. Acts of deliberate self harm in pre-adolescences led to higher rates of future behaviors.

Biological Factors

Studies have found that up to 90% of individuals who present with self harm meet diagnostic criteria for psychiatric disorders. The most common is depression, followed by substance use disorders and anxiety disorders (Skegg, 2005). General population studies have indicated that individuals with psychopathology are at increased risk of self harm and suicide. Individuals with antisocial and borderline personality disorders exhibit high rates of self harming behaviors. Eating disorders, schizophrenia and post traumatic stress disorder have also been found in study samples of self harmers (Skegg, 2005). Treating underlying psychopathology may reduce risk in affected individuals.

Table 1: Selected Risk Factors for Self Harm

1. Between puberty and old age
2. Female
3. Separated or divorced
4. Low socioeconomic status
5. Less education
6. Poverty

Skaggs, 2005

Deliberate Self-Harm (DSH) and Depression

While DSH is almost always associated with dysphoria, it is not always associated with the syndrome of depression. DSH can occur in the setting of depression associated with both bipolar disorder and unipolar major depressive disorder. Haw et al. (2001) when he looked at a cohort of 106 patients who presented to a hospital following an episode of DSH found that 92% of these patients had a psychiatric diagnosis and that the most common diagnosis was affective disorder (72% using ICD-10 criteria).

Early adverse life events have a major impact on subsequent mood states. Similarly, early adversity is a major correlate of subsequent DSH behaviors (Gladstone et al. 2004; Parker et al. 2005). Gladstone et al. (2004) examined DSH behaviors, personality characteristics, and childhood variables, including parental styles and childhood sexual/physical abuse, among 125 women with depressive disorders. Findings indicated that participants who were victims of childhood sexual assaults were more likely to engage in DSH as adults (Gladstone et al. 2004). In addition, respondents who were victims of childhood sexual abuse became depressed earlier in life than non-abused controls (Gladstone et al. 2004).

Adolescents with DSH generally have less severe depressive symptoms than individuals with suicidal ideation, but more severe symptoms than those without any history of self-injurious ideation. In a community sample, adolescents who have a history of self-harm reported more depressive symptoms than those without a self-harm history (Muehlenkamp et al. 2004). In a study of 218 adolescents, ages 13-19, who were receiving outpatient treatment for a depressive mood disorder, adolescents who had DSH behavior had less severe depressive symptoms than those with suicidal ideation or suicide attempts (Tuisku et al. 2006). Similarly, among adults the degree of seriousness of a self injurious act was associated with depression and with intent. In a study of 49 prisoners in Germany, measures of depression and hopelessness were both highly correlated with suicidal intent and lethality; less lethal methods were not correlated with depression (Lohner et al. 2006). Impulsive acts of self-harm were rarely associated with depression (Lohner et al. 2006).

DSH behaviors are not fixed over the life time. For example, 70% of 132 adolescents who had deliberately poisoned themselves and who were followed for 6 years stopped the self-harm behaviors within 3 years of the index event (Harrington et al. 2006). DSH continued into adulthood mainly among those with psychiatric disorders. Only 56% of these study participants had a psychiatric disorder, and the most common psychiatric diagnosis was depression (Harrington et al. 2006). DSH behaviors may appear de novo in the elderly.

Lamprecht et al. (2005) looked at older people presenting to an acute hospital with an episode of DSH. Sexual distribution among males and females was equal. Only 37% had a major depressive illness at the time of the DSH assessment, but 21% of the males had no psychiatric diagnoses at the time of the DSH (Lamprecht et al. 2005).

In young adults, the lack of depression in subjects with DSH has also been noted. Among 1,986 high-functioning military recruits (62% male), only 10% of those with a history of DSH reported depressive symptoms on the Beck's Depression Inventory (Klonsky et al. 2003). Peers viewed self-harmers as having strange and intense emotions and a heightened sensitivity to interpersonal rejection (Klonsky et al. 2003). Given that DSH may not necessarily be associated with depression, why does it occur? Tzemoz and Birchwood (2006) examined dysfunctional thinking patterns and intrusive memories in patients diagnosed with both unipolar depressive and bipolar mood disorders. They recruited 49 participants diagnosed with major depression, manic, or hypomanic episodes. Twenty healthy controls were also recruited from the same areas in Central England. Compared to the healthy controls, dysfunctional attitudes were abnormal in the mood disordered groups when ill (Tzemoz and Birchwood, 2006). Interestingly, whereas dysfunctional attitudes resolved in bipolar subjects as they became euthymic, they persisted into euthymia for those diagnosed with unipolar major depression (Tzemoz and Birchwood, 2006).

Deliberate Self Harm and Bipolar Illness

Intentional self harm in mania is rare and is probably related to the depressed mood that can occur during manic episodes (Ostacher and Eidelman, 2006). However, DSH during bipolar depressions is more common than DSH in unipolar depressive illness (Parker et al. 2005). Parker et al. (2005) reported that across samples of depressed individuals, more individuals with bipolar disorder tended to report DSH behaviors compared to those with unipolar depression. Smith et al. (2005) examined the prevalence rates of bipolar disorders and major depression among 87 young adults with recurrent depression; 83.9% of study respondents met criteria for major depressive disorder, 16.1% met criteria for a DSM-IV-defined bipolar disorder. The authors reported that among the respondents diagnosed with major depression, 45.7% had a history of DSH, and 13.0% had a history of a previous suicide attempt. Of the 14 respondents diagnosed with BP disorder, 71.4% had DSH and 28.6% had a history of deliberate self-harm.

One of the best known occurrences of DSH was performed by Vincent van Gogh (1853-1890), a Dutch Impressionist artist who had bipolar disorder (Jamison, 1993). On Christmas Eve in 1888, Van Gogh cut off his own earlobe with a razor blade as he was apparently attempting to attack an acquaintance. Following this episode of self-harm, van Gogh exhibited alternating states of "madness and lucidity," and received treatment in an asylum in Saint-Remy. Two months after his discharge from the asylum, he committed suicide by shooting himself "for the good of all" (Anonymous, 2007).

Mood Disorders and Suicide

Suicide, the act of ending one's life, is the most dramatic form of self-harm. Epidemiologic research indicates that in 2004, 31,484 individuals in the US died from suicide or self-inflicted injury (10.8 per 100,000 population) (Center for Disease Control, 2006). Extensive research has examined risk factors for suicide, and several studies have identified a history of prior suicide attempts as a very strong predictor of suicide risk (American Psychiatric Association, 2003; Borges et al. 2006; Gaynes et al. 2004). Certain sociodemographic characteristics have also been associated with high suicide risk. These include male gender, European-American ethnicity, and advanced age. However, the National Comorbidity Survey Replication Study, found that low income, "non-Hispanic Black" (p. 1750) ethnicity, and age less than 45 were significant correlates of suicide ideation (Borges et al. 2006). Additional risk factors include the presence of a psychiatric disorder, particularly depression, alcohol abuse, physical and sexual abuse, and a family history of suicide (Gaynes et al. 2004). Psychiatric disorders may be present in up to 90% of those who commit suicide (American Psychiatric Association, 2003). Divorced, separated, or widowed individuals have a higher risk of suicide (American Psychiatric Association, 2003). Conversley, high-conflict or violent marriages may increase the risk for suicide among married individuals (American Psychiatric Association, 2003).

Unipolar Depression and Suicide

Numerous studies have identified depression as a significant risk factor for suicide. This contributes to mortality rates associated with depression that are approximately 20 times higher than the general population (American Psychiatric Association, 2003). The fraction of people who have committed suicide that were depressed at the time of their death has been estimated to range from 15% (Rich et al. 1986) to 97.5% (Sinclair et al. 2005). However, most studies, including those that are based on psychological autopsies, estimate a rate of 30-34% (Arato et al. 1988; Henriksson et al. 1993; Foster et al. 1999). The fraction of adolescent suicides that involve depression may be slightly higher at 43% (Brent et al. 1999).

Co-morbid psychiatric conditions may additionally increase the risk for suicide. Paramount among these is co-occurring substance use which accounts for some 45% of completed suicides (Rich et al. 1986). Additionally, aggression (Dervic et al. 2006; Keilp et al. 2006) and cluster B personality disorders (Dervic et al. 2006) are associated with suicide attempts in depressed individuals with a history of childhood sexual abuse.

A decline in depression and hopelessness was associated with a decline in suicidal ideation in 198 people diagnosed with major depression (Sokero et al. 2006). There is a close correlation between the increased use of antidepressants and an observed decline in overall suicide rate (Korkeila et al. 2007; Gibbons et al. 2006), but this trend may have begun prior to the introduction of antidepressants (Safer and Zito, 2007). Antidepressants may have no effect on suicide ideation (Hammad et al. 2006) or may actually increase the risk of suicide attempt among depressed adults (Tiihonen et al. 2006) and suicide ideation among adolescents (Bridge et al. 2007; Dubicka et al. 2006), but may reduce completed suicides (Tiihonen et al. 2006). The United States Food and Drug Administration (FDA) has placed a warning on all antidepressants, that they may increase suicidal ideation in adolescents (Kuehn, 2007). While lithium is rarely used in major depressive disorder, it appears to have an anti-suicide effect, similar to that seen in bipolar illness (Guzzetta et al. 2007).

Vignette #2

John was a 61 year old male who presented to the emergency room with a 7cm laceration on his left inner forearm. The laceration was moderately deep and required multiple sutures.

There were no other signs of current or former abuse on his arms or the rest of his body. After John's arm was sutured, he was evaluated by a psychiatrist for a possible suicide attempt. John revealed that he was in a marriage that had not been healthy for quite some time and that his wife had called to say she was not coming home and that she wanted a divorce. John decided he could not face life without his wife and saw no way to call for help so cut himself. He denied suicidal intention at the time of the injury and denied it again at the time of the interview. John could not identify any social support persons and did not have any plans for the future. He kept insisting that he needed to go home but would not say what he needed to do there. John's past history was significant for physical abuse by his father when he was a child. His father then left when he was 11 years old. His mother was not emotionally available and was overwhelmed at being left with 4 children to care for when she only had a minimum wage job. John was on his own for most of his teen age life. As the oldest child, he was responsible for helping with the other 3 children when his mother was not around. John related that he had always thought the marriage to his husband was going to be different from his mother's and was not going to end in divorce. He said he felt like it was all his fault and he would never find another person to love him. John's psychiatrist felt that he was a risk for attempting suicide when he returned home and placed him in a psychiatric hospital for safety and stabilization.

Bipolar Disorder and Suicide

Lifetime prevalence of all bipolar disorders is approximately 2%; bipolar I disorder has a incidence rate of 0.8%, compared to 1.2% for bipolar II disorder. Suicide risk is high in bipolar disorder. Angst et al. (1995) followed 406 patients for 36 years; findings indicated that 11% committed suicide, regardless of whether patients were diagnosed with type I or II disorder. Other estimates approach 19% (Ostacher and Eidelman, 2006). The risk appears higher than in unipolar major depression. Chen et al. (1996) examined data from the Epidemiologic Catchment Area Study (ECA) to estimate lifetime rates of suicide attempts in mood disorders; findings indicated that 29.2% of respondents with bipolar disorder attempted suicide, compared to 15.9% among those with unipolar depressive disorder. Additionally, when subjects with bipolar disorder attempt suicide, the lethality of that attempt may be greater. Among 2,395 hospital admissions of patients with unipolar depression and bipolar disorder subjects with bipolar disorder had a higher incidence of more lethal suicide attempts (Raja et al. 2004). The odds of completed suicide in those with bipolar disorder is 2.0 times higher compared to those with unipolar depression (Raja et al. 2004). However, prevalence rates of suicide may be inflated, since researchers typically focus on hospitalized patients and those who have received treatment from a mental health provider. This self-selected population may be more ill compared to those who receive treatment from primary care providers, or those who do not receive any psychiatric treatment. Risk for suicide is highest during a depressive episode of bipolar disorder. Isometsa et al. (1994) found that among patients diagnosed with bipolar disorder, 80% of completed suicides occur during a depressive episode. Mortality from suicide in bipolar depression may be 30 times that of normal controls (Ostacher and Eidelman. 2006). However suicidal ideation and suicide completions may occur during the mixed (Dilsaver et al. 1994) or even manic phase (Cassidy et al. 2001). Rapid cycling also carries a higher likelihood for more serious suicide attempts but not an increase in completed suicides compared to other types of episodes (42 vs 27%) (MacKinnon et al. 2003). Suicide risk is highest in newly diagnosed bipolar patient. Fagiolini et al. (2004) found that among 104 patients with bipolar disorder, 50% attempted suicide within 7.5 years of the initial onset of the illness (either mania or depression). In these young

bipolar patients, suicide rarely occurs during episodes of mania. Lithium appears to have a clear effect on reducing completed suicide in bipolar patients with a five fold reduction in relative risk (Baldessarini et al. 2006; Tondo et al. 2001). More impressively, lithium reduces non-suicidal DSH and non-psychiatric mortality in bipolar patients (Cipriani et al. 2005).

Vignette #3

Dick was a 24 year old young man in law school when he had his first manic episode. He had a history of a depressive episode that had been difficult to treat when he was 18 but had not had any problems since that time and was not on any medications at the time of this manic episode. During the episode, he lost his job, his relationship with his girlfriend and he spent thousands more dollars than he could afford to spend in cars, jewelry, vacations and gifts to his girlfriend. He was hospitalized and stabilized on appropriate anti-manic medications. Approximately 4 months later, Dick began another depressive episode. This time he was thinking of all the things he had lost. He felt like his life as a lawyer was over and that he was destined to be a disabled person with no job, no family and no friends for the rest of his life. He did continue to take his medicines and see his psychiatrist but did not discuss any of these thoughts with any of his support persons. 2 months after the depressive episode began, Dick was found in his home, having hung himself from a rafter in the garage.

Serotonin System and Suicide

On a molecular level, the serotonin system has been implicated in self harm population studies. Low levels of 5 HIAA have been found in cerebrospinal fluid in self-harmers (Skegg, 2005). There are many biological associations between mood symptoms and aggression or violence. These include increased aggression with increased cytokine activity (Zalcman and Siegel, 2006), catecholamine metabolism (Volavka et al. 2004), testosterone (Pope et al. 2000), and hypothalamic-pituitary-adrenal axis dysfunction (Shea et al. 2005; Malkesman et al. 2005). However, the most consistent findings are with the serotonergic system.

Among the many findings associated with serotonergic dysfunction in aggression, platelet serotonin 2A receptor (5-HT2A) binding was increased in subjects with trait aggression (Lauterbach et al. 2006). Prefrontal cortical 5-HT2A binding was also increased in aggressive suicidal patients (Oquendo et al. 2006). Similarly, relative increases in plasma tryptophan levels (a precursor to serotonin) are associated with increased aggression and hostility (Lauterbach et al. 2006; Suarez and Krishnan. 2006) Lower CSF 5-HIAA concentration was independently associated with severity of lifetime aggressivity and a history of a higher lethality suicide attempt and may be part of the diathesis for these behaviors. The dopamine and norepinephrine systems do not appear to be as significantly involved in suicidal acts, aggression, or depression (Placidi et al. 2002). However, the most compelling findings regarding the involvement of serotonin in both mood disturbance and violence is found in the serotonin transporter polymorphisms.

Several recent studies have investigated the role of polymorphisms in the serotonin reuptake pump or the serotonin transporter gene (5HTTLPR). A common polymorphism of this gene is a deletion in the area of the gene that regulates its transcription into messenger RNA, and ultimately translation into expressed protein, the promoter region. Individuals with this deletion, called the short or "s" allele, express fewer serotonin transporters. Individuals who are homozygous for the "s" allele (ss), are more likely to develop depression (OR 1.5-179) (Cervilla et al. 2006) and depression after a traumatic event (Kaufman et al. 2004; Caspi

et al. 2003). Thus, the observed link between early life adversity, or later life trauma, and subsequent depression, is related, at least in part, to having the ss genotype (Kaufman et al. 2004; Caspi et al. 2000). While stressful life events or extreme adversity are clearly associated with subsequent depression, adversity is quite potent in inducing depression in subjects with the ss genotype; so that the dosage of adversity required to produce depression is much lower in individuals homozygous for the short form of the 5HTTLPR (Cervilla et al. 2007). Several studies have also found that the ss genotype is also associated with subclinical depressive symptoms in individuals without depression (Gonda et al. 2005, 2006; Gonda and Bagdy, 2006).

The ss genotype of the 5HTTLPR is also associated with aggression. In a case control study of conduct disorder with or without aggression, it was found that the ss genotype was strongly associated with aggression but not conduct disorder without aggression (Sakai et al. 2006). A positron emission tomography (PET) study of 5HRRLPR density found that reduced transporter density is associated with impulsive aggression (Frankle et al. 2005). While this study did not examine the genotype of the study subjects, it found that the phenotype that is expected with the ss genotype is associated with aggression (Frankle et al. 2005). Among schizophrenic patients who attempted suicide, the ss genotype of the 5HTTLPR was associated with violent suicide attempts but not with non-violent attempts nor with non-attempters (Bayle et al. 2003).

Psychological Factors

Many psychological factors may also contribute to self harm and suicidal behaviors. It has been suggested that rage towards others, feelings of abandonment, guilt or desperation may play a role in these behaviors at a subconscious level (Skegg, 2005). Poor problem solving skills, impaired decision making skills and factors that contribute to the former have been studied and indicated as risk factors in those who harm themselves (Skegg, 2005). Neuroticism, dissociation and novelty-seeking personality traits are associated with suicide and self harm (Skegg, 2005).

Direct Abuse or Neglect

Childhood abuse and neglect are clearly associated with a substantial increase in the risk for subsequent depression and maladaptive behaviors (Cukor and McGinn, 2006; Reigstad et al. 2006; Widom et al. 2007). This is true in all cultures in which it has been studied (Afifi, 2006).

Verbal and Emotional Abuse

The experience of verbal abuse during childhood (e.g., "you are stupid") increases depression, anger and hostility in young adults (Teicher et al. 2006; Sachs-Ericsson et al. 2006). Verbal and emotional abuse influence the development of self-concept, and lead to a self-critical style of cognitive processing that contributes to low self esteem (Cukor and McGinn, 2006; Sachs-Ericsson et al. 2006). This impaired self-image may be one of the underlying phenomena that increase the risk of subsequent sexual victimization as a young adult (Rich et al. 2005).

Physical Abuse

Physical abuse may be a major contributing factor in the development of violence in later life (Huizinga et al. 2006). Physical abuse is also pivotal in the development of depression in youths and on into adulthood (Widon et al. 2007; Cukor and McGinn, 2006; Reigstad et al. 2006; Wright et al. 2004). Physical abuse may occur in either the home environment or in school. Bullying is a form of verbal and physical violence that can have major impact on development. The odds of experiencing social problems, depression with suicidal ideation and attempts are 3.9 times higher among victims of bullying compared to non-victims (Brunstein Klomek et al. 2007; Kim et al. 2006). Furthermore, bullying behaviors have been linked to mood disturbances. The odds of bullies developing social problems, depression, and suicidality are 1.8 times higher compared to people who are not bullies, and bullies who are also targets of other bullies are 4.9 times as likely to develop social problems (Brustein Klomek et al. 2007; Kim et al. 2006). High profile school shooters, such as Columbine High School or Virginia Tech University, have been bullied by class mates.

Sexual Abuse

Sexual abuse of children is associated with a wide variety of physical and psychological sequelae, many of which are life-long. Early sexual abuse is associated with a significant increase in depression in both males and females (Peleikis et al. 2005; Conway et al. 2004; Gladstone et al. 2004; Martin et al. 2004). The risk of subsequent suicide attempts is 15 times higher in boys who experience early sexual abuse compared to non-abused boys (Martin et al. 2004); among women suicide ideation is 4.5 times higher (Masho et al. 2005). The consequences of childhood sexual abuse includes greater severity of depressive illness in adult patients over age 50 (Gamble et al. 2006; McGuigan and Middlemiss, 2005). Adult women who have experienced childhood sexual abuse are more likely to be victims of violence (Gladstone et al. 2004) and other forms of trauma, including sexual assault (Rich et al. 2005; Banyard et al. 2002). Sexual abuse perpetrated by adult women can be just as harmful as sexual abuse perpetrated by men (Denov, 2004).

Social/Cultural Factors

Experiences early in life may be an important risk factor for later self harm. Children of divorced parents, women of low education or socioeconomic status and children of parents with psychopathology are at higher risk of deliberate self harm (Skegg, 2005). Trauma early in life such as physical, sexual or emotional abuse and exposure to household violence has been identified as risk factors (Skegg, 2005). It has been difficult to determine if these experiences are independent risk factors, or if they lead to impairment in relationships that may also be a risk factor for self harm (Skegg, 2005).

Social support appears to play a key protective role in self harming behaviors as evidenced by groups of people who have been found to be a higher risk. Divorced and separated individuals are at a higher risk, as are unemployed individuals. It has been found that social support reduces self harming behaviors and moderate stress (Skegg, 2005). Multiple studies

have also found moral obligations and religious beliefs to be protective against suicide (Skegg, 2005).

20.4 Treatment

Risk assessment and the patient's ability to follow through with treatment are key factors in determining treatment modality in the suicidal patient. Depending on the circumstances, treatment can range from involuntary hospitalization on secure psychiatric wards to outpatient clinic follow-up. Treatment should be carried out in the environment that is least restrictive, but includes adequate measures for safety. Goals of management include establishing a therapeutic alliance, establishing safety and determining the patient's needs. Incorporating the patient's individual needs into the treatment plan is important to promote adherence (APA practice guidelines).

When establishing the therapeutic alliance, it is important for the psychiatrist to be aware of countertransferance and transference reactions between themselves and the suicidal patient. Dealing with suicidal individuals can uncover the psychiatrist's own feelings about death and suicide and may provoke anger in some. On the other hand, some patients with a strong desire to die may become angry at the treating physician, and others may have a desire to be saved instead of taking responsibility for their own actions (APA practice guidelines).

Attending to the patient's immediate safety is a priority in the treatment setting, especially in the acute phase. In the emergency setting, it is imperative to remove personal objects that the patient could use to harm themselves. Removing personal items such as purses and shoestrings that the patient could use to harm themselves may be necessary on inpatient units. Close surveillance via frequent safety checks or surveillance cameras may be necessary in acutely suicidal individuals (APA practice guidelines).

A balance between suicide risk and risk associated with hospitalization must be accomplished to determine the most appropriate setting. While establishing safety is a priority, there are also effects of hospitalization that may have negative effects on a patient's life situation. These include financial risks including hospital bills and lost time from work, social stigmatization and psychosocial stressors. Generally, hospitalization is indicated when patients are at high risk of self harm, have new onset of suicidal behaviors, require treatments that can only be performed in the hospital setting, or are unable to comply with less restrictive treatment options (APA practice guidelines).

Pharmacotherapy

Evidence clearly indicates that underlying mood disorders must be treated to optimize treatment in the suicidal or self-harming patient as discussed above in the pathogenesis discussion. A brief summary of findings regarding specific classes of drugs as related to self-harming behaviors is included below.

Antidepressants

According to the American Psychiatric Association practice guidelines, pharmacotherapy is commonly used in suicidal patients suffering from depression and anxiety disorders. They have also been used to treat suicidal patients with comorbid substance disorders. However, limited evidence based studies exist to support that this treatment modality reduces rates of suicide. Studies using FDA databases do not show differences in rates of suicide with the use of antidepressants (APA practice guidelines).

Conflicting evidence exists regarding the increased incidence of suicide following SSRI treatment. Several case reports were published, however, and patients should be educated regarding these findings. However, clinicians must be careful to not neglect treatment of real mood pathology due to fear.

Lithium

The APA practice guidelines identify treatment with lithium salts as an evidenced based treatment to reduce suicide risk in patients with bipolar disorder and major depressive disorder. They report that this treatment has been shown to decrease suicidal acts by 14-fold. Practitioners should be aware of the high lethality of overdose on lithium when prescribing quantities to potentially suicidal patients.

Other Mood Stablilzers

Anti-convulsant agents are frequently used as mood stabilizer therapy. They may reduce suicidal behaviors, however, are not as evidenced supportive as Lithium (APA practice guidelines).

Atypical Antipsychotics

Atypical antipsychotics are commonly used to reduce hallucinations, delusions, agitation, aggression and contusion, which may reduce self-harm and suicidal behaviors. These agents are indicated for use in patients with schizophrenia, schizoaffective disorder, and mood disorders with psychotic features. These include aripiprazone, clozapine, olanzapine, quitiapine, risperidone and ziprasidone. Clozapine is typically reserved for patients who do not respond to other agents due to side effects. For the same reason, typical antipsychotics are usually reserved for people not responding to newer agents (APA practice guidelines).

Antianxiety Agents

Theroetically, antianxiety agents would have the potential to reduce suicide and self-harm risk since anxiety is a risk factor. However, studies are limited. Agents commonly used are benzodiazepines and buspirone.

Psychotherapy

Since suicide is relatively rare in the general population, it is difficult to conduct studies with enough events to reach statistical significance. A meta-analysis of psychosocial interventions by Crawford et al. (2007) suggests that specific psychosocial interventions following acts of self-harm do little more than standard care to prevent subsequent suicide. Of the interventions studied, Cognitive Behavioral therapy appeared to have a trend towards reducing risk of suicide. Overall mortality in the intense intervention group was lower, however. Interventions that improve existing mood symptoms will ultimate reduce self destructive behaviors as discussed above.

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21 Forensic Psychiatry

Originally forensic psychiatrists were part of an obscure and small group of "alienists" who were dedicated to the study of mental conditions and their treatment among prisoners. At present they form part of an established and recognized group of super-specialists who have made deep incursions into the workings of the law and are transforming the practice of psychiatry. This influential status has not come without some misgivings about the basic identity of Forensic Psychiatry as a medical specialty and concerns about its utility and its ethics. Following definitional issues and a short historical review, this paper will describe modern developments of this specialty and comment on the ethical controversies surrounding its functions.

Forensic Psychiatry is a subspecialty of Psychiatry, which in turn, is a medical specialty. It is commonly defined as "the branch of psychiatry that deals with issues arising in the interface between psychiatry and the law" (Gutheil, 2004). Although short, to the point, and simple, this definition fails to emphasize that a good portion of the work in Forensic Psychiatry is to help the mentally ill who are in trouble with the law navigate three different, sometimes inimical, but interrelated systems: mental health, justice and corrections. Arboleda-Flórez (2006) has proposed a more encompassing definition that will cover the specific problems of managing the mentally ill offender: "Forensic Psychiatry is the branch of psychiatry that deals with issues arising in the interface between psychiatry and the law, and with the flow of mentally disordered offenders along a continuum of health and social systems."

Forensic Psychiatry is broad. Not only does it deal with matters related to criminal law, it also deals with civil law, and the development and application of mental health legislation. Unlike any other specialty in Medicine, including Psychiatry, where the work is done at the request of the patient and takes place within the confines of a highly private and confidential bilateral relationship between physician and patient, the work in Forensic Psychiatry is done at the request of a third party. The forensic encounter takes place in a triangular relationship that flows from the dictates of the Law that are binding on both the patient and the physician and on the agency requesting the assessment. These arrangements and the settings in which forensic psychiatrists do most of their work give the subspecialty three unique and clearly defined characteristics:

1. A specific clinical subject matter and management considerations

2. Knowledge of legal constructs and concepts in criminal law, civil law, and legislation

3. Working with a complex set of relationships within three social systems - medicine, justice and corrections.

21.1 Historical Review

A relationship between mental constructs and the Law has existed since antiquity and is already found in the Baba Ramma, an ancient codification of texts. In Egypt, Imhotep, the grand vizier of the Pharaoh Zoser may have been the first "medico-legal expert." In the Bible, the book of Deuteronomy makes reference to crime and punishment - God's punishment for transgressions of His commands was to visit on the violator "madness, and blindness, and astonishment of the heart" (mania, dementia, stupor).

The Romans codified the close relationship between mental states and the Law in the Corpus Iuris Civilis that contains a list of mental conditions that could serve as defense for criminal responsibility. Some other Roman legislation included the Twelve Tables, in which provisions are made for a system of guardianship of the insane; the Lex Aquila that exonerated those who caused damage not by negligence or malice, but by accident and the Lex Cornelia that excused children and the insane from punishment.

Henry de Bracton, around 1256, may have been the first legal scholar to attempt to identify the degree of legal impairment needed to exculpate an offender. In the first systematic treatise on English Law, written in the thirteenth century, he stated, "an insane person is one who does not know what he is doing and is lacking in mind and reason."

Medical experts were used in court proceedings in Bologna and other Italian cities during the XV century and in Freiburg, Germany. The scientific understanding of criminal behaviour and the expected legal proofs of wrongdoing as opposed to hearsay evidence were considered extensively in the Constitutio Carolina (1532). In 1654, Zachia, possibly the father of legal medicine, upgraded the Corpus Iuris Civilis with his Questiones medico-legales for use by the Sacred Rota, the highest judicial body of the Roman Catholic Church. In 1736 Matthew Hale published, posthumously, his History of the Pleas of the Crown in which he introduced the concept of partial insanity (Prosono, 1994).

Bracton's legal definition of insanity based on the concept of "does not know" still reverberates, as it constitutes the basic formula in the McNaughton rule, which is central to our current understanding of 'not guilty by reason of insanity'. The case of Daniel McNaughton in 1843 made history in the English world. McNaughton had a paranoid delusional system believing that the Prime Minister, Mr. Peel, was planning to make England go back under the authority of the Pope in Rome. In his attempt to kill the Prime Minister, he mistakenly murdered his private Secretary, Mr. Drummond. McNaughton was acquitted on the grounds of insanity, but not under the rules that bear his name. The finding prompted the Queen to ask a Panel of Judges for clarification of the rules for acquittal on the grounds of insanity, which resulted in the McNaughton rules for insanity defense that are in use in most of the English world even to the present. This rule based the determination of insanity on "lack knowledge of the act."

Forensic Psychiatry has grown exponentially since Bracton's times. Contemporary Forensic Psychiatry provides methodologies for the assessment of persons presumed to have some mental condition and who are caught in the midst of criminal or civil law proceedings. Forensic Psychiatry has benefited from four key important moments in legal-psychiatric thinking: 1. Increased knowledge of the relationship between mental illness and criminality. 2. Evolution of forensic legal operations in criminal and in civil law. 3. Developments in

systems interactions. 4. A deeper understanding and concern about issues in biomedical ethics.

These four moments underlie the expansion recently seen in Forensic Psychiatry from issues entirely related to criminal prosecutions and the treatment of mentally ill offenders to many other fields of Law and mental health policy.

21.2 Relationship between Mental Illness and Criminality

Worldwide, a wider understanding of the relationship between mental states and crime has led to an increased utilization of forensic experts in courts of law at different levels of legal action. The ways in which Forensic Psychiatry and Penal Law interface are varied and numerous within the criminal process, which expands from the moment of arrest to the time a convict finishes his or her sentence and is fully released back to the community. Forensic psychiatric systems could be called upon to work hand in hand with the justice/correctional system at each stage of the criminal process. At the moment of arrest the police could divert a clearly mentally ill person to a hospital emergency for assessment and treatment if required, including possible hospitalization, or detain the person and proceed to book for an appearance before a magistrate or lower judge. The judge could keep the person in a jail pending a decision, or, depending on the case, the accused could be transferred to a higher court. At this stage the accused could be found innocent and released, an assessment could be ordered to determine fitness to stand trial or criminal responsibility (vide infra), or the person could be found not criminally responsible because of a mental condition. Finally, the person could also be found guilty and sentenced to a prison term.

The multiple entanglements between psychiatric systems and the legal system are based on the recognition in traditional legal doctrine and contemporary public policy that a population exists in which mental disorders are related to criminal behaviour. In fact, in many jurisdictions, mental health legislation makes dangerousness associated with a mental condition, or the potential to cause grievous bodily harm to self or others, the main criterion for civil commitment (Appelbaum, 1994; Arboleda-Flórez and Copithorne, 1998). Criminal Codes in most countries also assume that a relationship exists between mental states and criminal offending and that this relationship may be determinative in the outcome of a commitment hearing or criminal trial. Whether this putative relationship between crime and psychopathology is causal or one of social convenience is a matter of much controversy given some convergence between the two sets of phenomena (mental illness and criminal behaviour) and specific legal procedures that apply to mentally ill offenders.

With respect to convergence, it is important to differentiate clinical pathology from criminal behaviour. While socially abnormal behaviour should not be automatically considered a manifestation of mental illness, there are mental disorders whose very behavioural manifestations are, ipso facto, criminal offenses. For example, persons affected with sexual disorders, firesetting and compulsive stealing become criminal the moment their symptoms are expressed, because the symptom is a criminal act. In these cases, the convergence between symptom and criminality is absolute.

In many other disorders, symptoms can be expressed without necessarily breaking the law, such as in addictions, personality, or impulse control disorders. Any convergence in these

disorders flows through other social and legal considerations. For example, in some countries mere possession of alcohol is an offense.

Finally, in most cases, convergence is not straightforward. An example is the presumed relationship between serious mental illnesses (such as schizophrenia or depression) and violence toward others. The vast majority of people experiencing these disorders never commit an act of violence or a criminal offense. Indeed, they are more often the victims of violence than the perpetrators.

In most countries specific legal procedures apply to persons charged with a criminal offence, but who may be also mentally ill. These procedures form part of Criminal or Penal Law, the section of the Law that deals with criminal sanctions for crimes against property or persons. As the State has an interest in protecting its citizens, breaches of the law affecting a citizen imposes an obligation on the State to find the culprit and bring him or her to justice. While the aggrieved citizen may not be seeking revenge, it is important to demonstrate that justice has been done and that perpetrators are properly punished. Criminal Law relates to regulations and sanctions the Law prescribes to lawbreakers whether for misdemeanors or felony offences and the ways in which exculpatory reasons such as mental illness could be used to minimize the punishment.

Exculpatory procedures based on the presence of a mental condition are based on the fact that there are occasions when mental illness could negate one of the two elements required by law to judge the accused. The first element is an acknowledgment by all involved that a crime has been committed, actus reus, and that the accused most probably did it. The second element is a considered decision by the Judge alone or with the help of mental health experts, that the act not only took place, but that the perpetrator had the full intention and was fully conscious of what he or she was doing at the time the act took place, besides being aware of the consequences of the act. This is known as having a guilty mind or mens rea. A forensic psychiatric assessment is usually requested if there is any doubt that the person was mentally ill at the time the offence took place, or mentally ill at the time the person appears in court.

21.3 Forensic Legal Operations in Criminal Law

There are three major areas in Criminal Law that need consideration as it pertains to the involvement of forensic psychiatrists – fitness to stand trial, criminal responsibility and dangerous offender applications.

Fitness to stand trial pertains to the condition of the accused at the time of the trial and is a legal requirement found in countries that follow the Anglo-Saxon common law system, but it is also found in other legal systems. On appearing in court to face a charge, the law presumes that everybody is fit (or mentally competent to stand trial), but if the court is presented with information that the accused may be mentally ill, it may request a psychiatric examination. If the person is found to be seriously mentally ill the court will order a transfer to a psychiatric institution for an in-patient assessment. The decision that the person is not fit to stand trial remains always on the court, but the forensic psychiatrist is expected to provide an opinion about whether the person suffers from a mental condition, and whether that mental condition affects the parameters of fitness. These parameters are rather simple;

in most countries all it is required is to determine whether the person, on account of the mental condition is unable:

1. To understand the nature and object of the legal proceedings
2. To understand the possible consequences of the proceedings, or
3. To communicate with counsel.

A ruling that the accused is not fit (or competent) to stand trial triggers a decision by the court to transfer the accused to a psychiatric facility with the expectation that treatment will restore competence. The question for clinicians revolves on what parameters to use to predict restorability of competence, which relates to an adequate response to treatment.

Assessments for fitness to stand trial, or capacity for processability, are a frequent reason to request a forensic assessment. Persons who are mentally ill at the time of trial cannot be tried; the trial stops until the person improves or regains his sanity. A person cannot be tried in absentia, meaning the person has to be present, or be properly represented by counsel, at the time of the trial. Being present means both physically and mentally present because it is assumed that if the person is mentally ill, it is tantamount to not being present in the proceedings, the mind being somewhere else. To this end, the person may be remanded to a forensic facility and it is expected that, once treatment is instituted as improvement takes place, the person will be returned to court as competent and the trial will continue. As in many other forensic functions, diagnostically, the issue is not whether the person has a particular mental condition, but whether current symptoms would preclude the continuation of the trial.

Criminal responsibility is a legal construct that intends to gauge the mental condition of the accused at the time of the offence. Ingrained in most legal systems is the concept that offenders who are mentally capable at the time of trial, but who were mentally ill at the time the offence was committed, are to be managed through other dispositions than those that apply to any other regular offender. To this effect, once the issue of fitness to stand trial is decided, the next step in the process is to assess whether the accused was the perpetrator of the crime. This step ends with a finding of innocence or guilt. On the assumption that the accused was indeed the culprit the process tries then to determine a level of responsibility to ascribe for the unlawful behaviour. If the accused could demonstrate that, at the time of the offence, his or her mental faculties were impaired by virtue of mental illness, the court may find that requirements to establish a guilty mind (mens rea) have not been met and proceeds to apply insanity regulations as stipulated by the law. These regulations include the legal tests used to decide the level at which a mental condition has impacted on competence to know, to understand or to appreciate the nature of the crime with which the person is charged. A finding that the competence of the accused was severely affected leads to a declaration that he or she was "not criminally responsible because of a mental condition," or similar wording such as "not guilty by reasons of insanity."

Forensic psychiatrists are often required to advise the court about the level of criminal responsibility to be ascribed to the accused. A finding of not being criminally responsible implies that the person committed the act (actus reus), but is nonetheless, absolved in the eyes of society for not having a guilty mind (mens rea); such a finding precludes criminal sanctions. Criminal responsibility is a social construct and cannot be measured scientifically; it is only the judge or jury that can decide what level to ascribe to the accused.

In some countries the issue in law is to decide whether an accused should be considered imputable. Imputability differs from criminal responsibility in that it refers to the fact that the accused, on account of suffering from a mental condition, cannot be considered as capable of having committed the crime. The concept derives from Roman law where "demens, furiosus et mentecaptus" (demented, maniacs and mentally retarded) as well as infants below the age of seven were considered incapable of having the malice aforethought to form the intent to commit a crime. If the person was lacking malice and intent, then, he or she could not be imputed with authorship of a crime. Forensic psychiatrists are often required to arrive at these diagnostic decisions.

As in the case of fitness to stand trial, the basic element of a determination on criminal responsibility is not whether the person had a mental illness at the time the offence was committed. Rather, what is important is to determine whether such illness was severe enough so as to produce incapacity to meet the elements required to establish criminal responsibility, partially or totally. It is for the mental health specialist to evaluate whether the accused had been mentally ill at the time of the offence, but it is for the court to decide whether the mental illness had produced an incapacity that rendered the person not criminally responsible. The role of the mental health specialist is to conduct an in-depth assessment of the personality and mental condition at present and of the claims that the accused was mentally ill at the time of the offence, and, then, to gauge the severity of the incapacity that it might have caused so as to be able to advise the court appropriately.

Legislation to determine the level of criminal responsibility or similar legal concepts is found in the laws of every country. In many of the countries that follow the common law system the test of criminal responsibility follows the McNaughton Rules of Insanity or a variance of the same. The most important of these rules reads: To establish a defense on the ground of insanity it must be clearly proved that at the time of the committing of the act the accused party was labouring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing; or, if he did know it, that he did not know he was doing what was wrong.

A decision that the accused was not criminally responsible triggers the application of special disposition measures. Legislation in many countries dictates that persons who are found not criminally responsible should be sent to special facilities "for the criminally insane" for treatment, supposedly, until the person gets better. In practice, the determination that the person has improved enough to be released to the community is vested on semi-autonomous quasi-judicial Boards, on the courts, on a political appointee, or as in some countries, on the psychiatrists at forensic wards of mental hospitals. Once sufficient improvement has been observed, the person could be released, but would be expected to follow treatment arrangements in the community with enforced compliance under condition of returning to hospital if a relapse occurs or if the person is not compliant. In some advanced mental health systems and depending on the seriousness of the offence and the severity of the mental condition, a court of law may decide not to send the accused to a hospital, but to issue a community treatment order whereby the person abides to enter into a treatment program as specified by the court and under the control of some quasi-judicial body.

Apart from very young children who are deemed not to have the necessary requirements to form a guilty mind by virtue of their emotional and neurological immaturity, everybody else is deemed to be responsible unless proven otherwise based on the presence of some mental

condition. The law provides for a gradient for criminal responsibility, from none at all to fully responsible (Arboleda-Flórez and Deynaka, 1999).

Points to remember

FITNESS TO STAND TRIAL

CRIMINAL RESPONSIBILITY

1. Mental illness at time of trial

2. Everybody is deemed to be fit unless the contrary is demonstrated

3. There are two elements - mental illness and resulting incapacity

4. Incapacity is the determinative factor

5. Basic elements pertain to capacity to understand basic issues of law at the time of trial such as nature of the proceedings and the consequences that could flow from them, and to communicate with counsel

6. If the person is found unfit and is not dangerous, the legal proceedings could be discontinued or stayed on minor charges

7. Otherwise, the trial stops and the accused is remanded for treatment until well enough to return to trial

1. Mental illness at time of offence

2. Everybody is deemed to have mens rea unless the contrary is demonstrated

3. There are two elements - mental illness and resulting incapacity

4. Incapacity is the determinative factor

5. Basic elements pertain to mental condition at time of offence severe enough so as to render the person unable to know or to appreciate that he or she is committing a crime, or unable to form the specific criminal intent

6. The person is sent to a hospital for treatment or is placed on a community treatment order according to mental condition and seriousness of offence

7. Eventually, the person could be released from state control.

Finally, the third important function in criminal proceedings and one that requires a major involvement of forensic psychiatrists is the determination of whether a particular offender is dangerous. Dangerous offender applications demand a high level of expertise on the part of forensic experts who are expected to provide courts with technical and scientific information on risk assessment and prediction of future violence, especially dangerous sexual offending. Dangerousness determinations rely heavily on a thorough assessment of the personality of the offender, a history of violent behaviour and responses to specific scales intended to measure risk. Many clinicians are of the opinion that the probability of risk to reoffend is particularly high among certain types of personality and when the last offence is a continuation of the same pattern of escalating violent behaviour in both frequency and severity. In these applications, the focus is on a history of violent behaviour and

the likelihood that it will continue in the future, not the specific diagnosis of a mental condition—although again the diagnosis of some mental disorder may be a requirement for entry into the system. Likelihood of future violence is determined through an in-depth forensic psychiatric assessment that includes thorough forensic examinations, neurological examinations, neuroimaging and the application of a series of specialized instruments in the form of tests and scales. Two of these instruments have received worldwide attention, the Hare (1991) Psychopathic Checklist (PCL-R), and the HCR-20 (History, Clinical, Risk – 20 questions) devised by Webster (1996). While the former is more appropriate for long-term predictions regarding psychopathic offenders, the latter is more in use for the management of regular mental patients in clinical settings. Despite claims to more objectivity, these instruments, like other predictive instruments that use clinical and prospective variables, rely heavily on the clinical insights and technical skills of the clinician.

Mental patients have traditionally been considered prone to violence, but results from research on whether mental illness causes violence per se, or whether violence is only associated with mental illness through a host of different variables such as age, gender, or socio-economic status has not yielded a definite answer. It is acknowledged, however, that some mental patients who suffer from particular mental conditions alone or in combination with substance abuse disorders, or comorbid with antisocial personality disorders, or those whose mental symptoms over-ride personal controls could be more violent than other mental patients, or the population at large.

The courts expect that forensic psychiatrists are in a position to provide advice on proper venues for disposition once an offender is found not fit to stand trial, not criminally responsible on account of mental illness or is deemed dangerous. The task for forensic psychiatrists in these situations is to gauge the level of systems interface in relation to different types of receiving and treating institutions. Hospitals for the criminally insane, mental hospitals for civilly committed patients, penitentiary hospitals for mentally ill inmates, as well as hospital wings in local jails, are all part of the mental health system, and their interdependency has to be acknowledged for purposes of system integration and budgeting. How mental patients are managed in prisons systems is also a major matter of concern. Deterrence, punishment, rehabilitation, retribution and incapacitation are among the reasons usually given for the need to impose a sentence. Of these, the one that would most directly involve mental health professionals is rehabilitation, especially because mental illness is rampant in prison and many jails or penitentiaries are practically extensions of the mental health system (Konrad, 2002). In particular, jails in some communities are part and parcel of the local mental health system. Estimates of prevalence of mental illness among inmates in some systems go as high as 65% in any given year. Policies of deinstitutionalization have been blamed for the large number of mental patients in prisons in that having closed the mental hospitals no alternatives have been provided for them in the community. Thus, rather than the actual policies to relocate mental patients back to their communities the real culprit seems to be improper implementation of the policies and lack of adequate resources.

Apart from regular mental conditions among prisoners many of whom having been mentally ill prior to be sentenced to a prison term, prison environments do produce special mental problems. Research on these problems has a long history. Considerable work was done in Germany during the nineteenth century on suicide in prisons, the prevalence of mental conditions among prisoners, and the influence of the prison environment as a risk factor to psychiatric illness. The term prison psychosis originated from that research; it describes

an acute psychotic breakdown as a result of the highly stressful situations in the prison. Equally, members of the same school of German prison research, described Ganser Syndrome, a peculiar syndrome in which the person appears confused and psychotic and gives answers that are approximate or "past the point" of the question, such as answering that a chair has three legs instead of four. This syndrome is transitory and has been classified as a form of pseudo-dementia.

The high proportion of individuals who are seriously mentally ill in prison environments is a source of major administrative concern. Mentally ill prisoners have to be housed in an institution that is not typically mandated or funded to provide clinical services. Their needs compete with many other more pressing needs in prisons and resources have to be allocated that are taken away from other health priorities within the system such as treatment for prisoners who suffer from AIDS, hepatitis, tuberculosis, or sexually transmitted diseases. Mental patients often require specialized correctional measures to protect them from suicidal behaviours, from being abused or assaulted by other inmates, or from assaulting others. In general, mental patients in prisons require extra services and higher staff ratios, but the attention given them can never compare with the quality of care at mental hospitals or at psychiatric units in general hospitals.

Forensic psychiatrists are usually in charge of conducting assessments and providing treatment to mentally ill inmates, but their jobs continue once the inmates are released into the community. On exit from the legal-correctional system forensic psychiatrists are expected to provide expert knowledge on matters such as readiness for parole, predictions of recidivism, commitment legislation applicable to offenders about to be released, the phenomenon of double revolving doors for the mentally ill in prisons and hospitals and treatment of ex-inmates in the community.

The need for forensic psychiatric services in all these justice/correctional activities is dictated by the close relationship between the two systems that have developed over the years out of the realization that the population served by both psychiatry and corrections is often one and the same. Many ethical, political, and human rights issues arise out of these situations, but with proper controls and safeguards in the system, compassionate and enlightened programs could be developed and implemented in forensic settings and long stay mental hospitals while community alternatives such as half-way houses could be sought to replace long term institutionalization without impacting on the safety of the public.

21.4 Forensic Legal Operations in Civil Law

Civil Law is defined as the body of legal decisions, in Common Law countries, or rules and regulations in those countries that follow Romano-Germanic systems of law that govern the relationship among individuals. Ordinarily, breaches of those rules by one person against another cause conflicts that often end up in courts for adjudication. Psychiatrists and other mental health specialists are regularly required to conduct assessments with a view to determine the presence of mental or emotional problems in one of the parties. However, most issues arising out of Civil Law that require mental health assessments pertain to the individual having lost the ability to manage particular situations or to discharge particular functions. At play are two major concepts, capacity and competence. Although there is a tendency to use these two concepts interchangeably, they are not the same. In general,

capacity refers specifically to the presence of physical, emotional and cognitive abilities necessary to make decisions or to engage in a course of action. Competency, on the other hand, refers more specifically to the legal consequences of not having capacity. In these definitions, "capacity" is a medical function whereas "competency" is a legal decision; while capacity refers to symptoms affecting the individual, competency refers to the impact those symptoms may have on legal and social standing. Capacity has also been defined as the ability to make an informed choice with respect to a specific decision, and competence as the ability to process and understand information and to make well-circumscribed decisions based on that understanding. As is obvious, these definitions ascribe to both concepts a legal determinism together with expected teleological consequences. Whatever the definition, however, in the end, a determination of incapacity leading to a finding of incompetence becomes a matter of social control that is used to legitimize the application of social strictures to an individual.

Assessments of capacity and competence are needed in multiple situations that range from cases when psychiatric assessments are required in order to specify the impact and emotional effects of injuries on a third party involved in a motor vehicle accident to capacity to write a will or to enter into contracts. These determinations could also apply to psychological autopsies in order to assess testamentary capacity on suicidal cases or cases of sudden death, or evaluations for fitness and incapacity to work and, of late in many countries, evaluations to determine access to benefits contemplated in disability insurance. In most of these situations the issue at hand is a determination of capacity and competence to perform some function, or the evaluation of autonomous decision making by mentally ill persons, impaired persons or those who have suffered brain damage or are affected by dementia.

The United Nations Declaration on Human Rights, Paragraph 6, states that everyone has the right to recognition everywhere as a person before the law. However, having inherent legal rights is not the same as having legal capacity to benefit from them, since this capacity may be compromised among persons suffering from mental disorders. Given the importance of being able and allowed to exercise one's rights as an assertion of personal autonomy, any abrogation of that power generally requires a judicial decision. Hence, in most instances (medical treatment settings sometimes constituting an exception) a medical decision that a person has lost capacity enters into effect only after a legal determination of incompetence has been completed.

There is always a presumption of capacity; a person is assumed to be capable and competent to make decisions unless proven otherwise. Decision making capacity requires an ability to understand, to appreciate, and to reason about the relevant information or situation confronting the person, to make an informed choice and to be able to communicate it. Clinicians rely on their clinical knowledge, their judgment and on special scales to make these assessments. However, the presence of a major mental or physical condition does not in and of itself produce incapacity in general or for specific functions. Even in the presence of a condition that may affect capacity, a person may still be competent to carry out some functions, not just because capacity fluctuates from time to time, but also because competence is not an all or none concept. Competence is tied to the specific decision or function to be accomplished. For example, a stroke may render a person incapacitated to drive a motor vehicle and, therefore, incompetent to drive, but the person could still have the capacity to enter into contracts or to manage personal financial affairs. With time and proper rehabilitation, the person might be able to regain capacity to drive. Given that

incapacity is often time-limited, findings of incompetence should be reviewed at appropriate intervals. Although the subjects of capacity evaluations should be informed of the purpose of the assessment, consent is not typically required for an evaluation to be completed. Capacity assessments are protracted and take time so it is advisable to use a screening test of capacity and to do a full assessment only if the person fails the screening test. This will reduce the burden on both the subject of the assessment and the evaluator if the screening test is passed. As is the case in criminal law, in civil law what is important is not just a diagnosis—which here may not even be required as a threshold determination—but the incapacity to execute some functions caused by the symptoms of the medical condition. For example, persons suffering from a serious bipolar disorder may during the manic behaviour enter into dubious business deals or spend foolishly the personal or the family fortunes. Under these circumstances the person could be declared incompetent to make financial decisions until the manic symptoms are brought under control. Not to take this step may leave the medical practitioner open to litigation for negligence.

The legal tests for competency are usually defined in broad statutory phrases that are, at times, difficult to operationalize. When conducting incapacity evaluations, clinicians should examine whether the patient:

a) Understands what the problem is

b) Knows what the matters under potential litigation are and why

c) Knows the facts in relation to matters being questioned (whether financial, custody of children, health, etc.) d) Is able to process information in a factual and rational way, and

e) Can function in his or her regular environment.

Clinicians should, then, assess the demands of the environment on the person, the adequacy of the sources of information, and whether more examinations or tests are required. The gist of the evaluation is not only to determine the presence of incapacity, but also to evaluate how best the person could cope under the circumstances, what aides would be required to help the person cope better, and how best to protect the interest and rights of the person. As such, competency evaluations tax the clinical knowledge of the expert as well as his ethical qualities and his knowledge of the systems and resources available in the community.

A determination of incapacity (a medical function) that could lead to a finding of incompetence (a legal decision) legitimizes the restriction on the person's powers to make autonomous decisions. Given the serious consequences of a decision of incompetence on a person's autonomy, clinicians have an ethical duty to base their decisions on the best available clinical evidence.

21.5 Systems Interactions

The double revolving door phenomenon whereby mental patients circulate between mental institutions and prisons has made forensic psychiatrists deeply aware of the interactions in the mental health system and the links between this system and the justice and correctional systems. By virtue of their involvement in legal matters forensic psychiatrists have developed a major interest in the drafting and the application of mental health legislation, especially on the issues of involuntary commitment that in many countries is based on determination

of dangerousness (application of police power) as opposed to just a need for treatment (parens patriae) concepts. In addition, forensic psychiatrists are asked for expertise in the management of mentally ill offenders and assessment of legal protections for incompetent persons. Given that one major area of their expertise is the assessment of violence and the possibility of future violent behaviour through the evaluation of dangerousness via risk assessment and risk management methodologies, forensic psychiatrists are usually called upon to make decisions on risk posed by violent civilly committed patients. Issues of coercion and protection of human rights of the mentally ill are often major considerations to take into account during these evaluations (Arboleda-Flórez, 2008). Protection of human rights and the acceptance that deprivation of liberty should be only a matter of last recourse has led some jurisdictions to implement special laws for outpatient commitment. These regulations enjoin the patient to accept and comply with special conditions in order to remain free, such as accepting treatment in the community.

There is a close interaction between legislation and the development of adequate mental health systems, and the delivery of care whether in institutions or in the community. Mental health legislation with overly restrictive commitment clauses even for short-term commitment, deinstitutionalization resulting from the closure of old mental hospitals, changes in health care delivery systems towards short admissions to general psychiatric units and subsequent treatment in the community, and the large number of mental patients that end up in jails have created in many countries a sense that the mental health system is adrift. The growth of Forensic Psychiatry may be due to changes in the law and to a more liberal acceptance of psychiatric explanations of behaviour, but a more immediate reason may be the large number of mental patients in forensic facilities, jails, prisons, and penitentiaries. Failures of the general mental health system may, therefore, be at the root of the growing importance of Forensic Psychiatry.

21.6 Ethical Issues

Several ethical concerns arise from the involvement of forensic psychiatrists in so many social, clinical and legal areas as have been mentioned in the sections above. Much ethical debate has resulted about the propriety and ethical imperatives that might be trampled during so many forensic functions and interventions. Stone (1984), for example, felt so concerned about what could take place that he even opined that it was improper for forensic psychiatrists to appear in legal forums and that to do so would indicate that they were not acting as physicians. Waving such a threat of excommunication from the medical fold, Stone compels forensic psychiatrists to abandon all legal premises. To the contrary, Griffith (1998) felt that to do so would be a veritable calamity to vulnerable populations that could expose them to unnecessary hardships and possible abuse. Appelbaum (1997) took a more conciliatory path and sought to satisfy the queasiness and concerns manifested by Stone by producing a model based on the principles of truth-telling on entrance at the moment of the forensic encounter and subsequent respect for the person undergoing the assessment (Arboleda-Flórez, 2005).

Important as these theoretical lucubrations on the ethics of forensic psychiatry are, for purposes of this paper only three practical matters will be considered – those relating to expert testimony including the ethical virtues and the skills of the expert and the quality of

the expertise, issues arising from double agentry situations and the matter of research on prisoners.

Expert testimony imposes on forensic psychiatrists an obligation to keep updated on clinical knowledge and on the latest results from research on the subject matter of the particular case. The forensic expert is considered a master in the application of the medico-legal method that entails deep knowledge of medical issues and legal operations. Preparation of a legal report or, specially, verbal presentation of evidence, is tantamount to an examination in public of the practitioner's depth of knowledge and actualization. Expert evidence demands also that the forensic expert be up to date on issues of research and on technological aids such as laboratory tests or psychological scales that are often used to arrive at a diagnosis. Forensic practitioners should make a point of knowing in detail the scientific bases of those technologies.

Knowledge per se is no guarantee that the expert is an ethical person, as this virtue comes from other constructs in the personality make up of the practitioner, however, it is worthwhile to mention some expected virtues in the application of the medico-legal method. It is expected that the forensic psychiatric expert be aware of the importance of the expert role, the need for rigorous preparation and methodical exploration of alternative conclusions, and the need to anticipate the challenges to be presented at cross examination in court. In addition, experts should also strive to embody the following qualities:

a. Objectivity in interpreting material evidence

b. Impartiality in elucidating truth regardless of the interests of the parties in conflict

c. Veracity, regardless of social, political or legal consequences

d. Knowledge and skills in clinical evaluation

e. Analytical capacity to correlate clinical findings with the legal question

f. Common sense and application of the law of parsimony (Ockham's razor)

g. Keen critical abilities to avoid assuming extreme positions, premature closure of alternative explanations or believing in the infallibility of one's clinical findings

h. Excellent grounding in biological, medical and social sciences

i. Good understanding of legal concepts and terminology, and

j. Grounding and a clear understanding of the ethical conflicts in forensic psychiatry.

Ignorance of relevant medical or legal facts, inability to remain neutral, dishonesty and blindness to the ethical quagmires of medico-legal work are incompatible with the role of an expert.

Knowledge is a sine qua non condition to determine the quality of the skills the expert brings to an evaluation including being able to choose the best tools required for the assessment and striving to recognize secondary gain for the expert or for the person being evaluated. Hence, forensic psychiatrists need to verify their conclusions whenever possible via information from third parties, including witnesses, family and friends, who can describe the behaviour of the defendant or litigant, the psychiatric history, and the person's mental state at the time in question. Efforts should be made to obtain school, military and hospital records and any other documents that could shed light on the development and the presence of symptoms

and on the veracity of the client. Similarly, in a quest for objectivity in the diagnostic formulation, clinical aids to diagnosis, such as electroencephalogram, diagnostic imaging, laboratory tests and psychological tests are often indicated. The more the expert bases his conclusions on objective information, the better grounded are likely to be the diagnosis and the conclusions. Finally, quality of the expertise involves quality in the preparation and presentation of the psychiatric legal report.

Double agentry refers to the fact that forensic specialists usually see clients who are referred by some agency requesting the evaluation. The most frequent case is that the person is referred and is under some kind of coercion to attend, or expects that a report will be produced for the referring agency. Very often, the payment for the evaluation is made by the agency, or the forensic expert is on the hire of the agency. This makes it impossible not to have a double allegiance, which an ethical practitioner should openly explain to the patient right from the outset of the evaluation. It would be expected that the practitioner has cleared his involvement with the agency and requested complete independence in the way the evaluation is to be conducted and to arrive at conclusions through a systematic search for answers and to present them even if they are negative to the interest of the hiring agency. Forensic psychiatrists should always be aware that they could not trespass ethical rules no matter what the demands of the master. Less than that would make of the practitioner a simple hire gun or unscrupulous operator.

Finally, in regard to medical research among prisoners it should be kept in mind that research is an area in which major ethical transgressions have occurred throughout history. Books on medical ethics are full of examples about abuse of patients who are at the same time subjects of research, usually at the hands of their own treating physician. Abuse of prisoners as subjects of research has not been an exception. Prisoners have been seen as potential research subjects and have been taken advantage of by providing incentives amounting to trinkets or by abusing their status as a vulnerable population given their condition of subjugation and living in a situation where autonomous decision making would be questionable. Prisoners may have the capacity to make a decision to become a subject of research, but doubts could be raised about whether such decision was entirely voluntary.

An ideology of good for science as being a higher value over the deprivation and suffering of few persons seems to have been at the base of the interest to use prisoners as subjects of research. This ideology would justify the conduct of experiments on human beings without the much needed respect for their autonomy. This was the ideology that was in place until the end of the Second World War, when, under the impact of the horrors practiced by Nazi doctors (Aziz, 1976) steps were introduced to control research among prisoners and to establish ethical guidelines binding the researchers. In the United States, for example, concerns about abuse of prisoners for purpose of research led to the appointment of a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1976. Recommendations of this Commission include that only prisons characterized by a great deal of openness could allow their inmates to be involved in research, that the prisoner-research subject should enjoy the exercise a high degree of voluntariness and that prisoners should not be deprived access to experimental drugs, if so needed, on account that prisoners are a vulnerable population. This last recommendation was essential in order to strike a just balance between the protection of the prisoner as a subject of research and his or her capacity and competence to make a considered decision to participate in research. The vulnerable status of a prisoner does not prevent participation in research for as long

as proper guarantees are in place to prevent abuses. The problem of prisoners becoming subjects of research gets further complicated when so many of them (as described in an earlier section) are also mentally ill. In these cases a double vulnerability will be present, mental illness that may affect capacity and competence decisions and imprisonment that may affect that ability to make them voluntarily. Prison administrators should be more vigilant and take extra-precautions to prevent possible abuse of mentally ill prisoners as subjects of research

21.7 Conclusions

Following a historical review to ground the development of Forensic Psychiatry, this paper has dealt with the scope of this specialty and with ethical issues confronting its practitioners. The paper has enumerated four moments in the development of legal-psychiatric thinking. The first two moments - evolution in the understanding and appreciation of the relationship between mental illness and criminality and impacts of mental illness on lawful behaviour were applied to underline the increasing scope of Forensic Psychiatry in practically all areas of Criminal Law and in a large number of situations in Civil Law. The third moment on systems interactions examined issues on the navigating of mentally ill offenders within the three systems of medicine, justice and corrections. Finally, on the last moment, pertaining to ethics, this paper dealt with issues arisen from the functions of forensic psychiatrists as expert witnesses, the problems with double agentry and the potential for abuse while conducting research on prisoners.

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